Principles of
INTERNAL MEDICINE

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NCIPLES OF INTERNAL MEDICINE

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To all those who have taught us
and especially to our younger colleagues
who continue to teach and inspire us

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Preface

One of the initial purposes of this book was to provide for the medical student a certain unity between reading and instruction *During the second* year training in history taking and in physical diagnosis involves an approach to the manifestations of disease At the same time the application of the basic sciences to clinical problems is clarified as he studies disease mechanisms In the third and fourth years he cares for patients with specific diseases It seemed to us desirable that there be a text which presents internal medicine in the way that the subject is approached in the curriculum

We also believe a discussion of the main symptoms of disease and of their mechanisms is useful to the practicing physician who logically thinks of specific diseases only after he has first correctly interpreted the meaning of a patient's symptoms These considerations led us to continue in this edition the same general arrangement adopted for the preceding ones

For the third edition the book has been reset completely and its organization somewhat modified Part Two Cardinal Manifestations of Disease has been thoroughly revised The sections dealing with disorders of circulatory and pulmonary function have been rewritten in order to bring them into line with the rapid advances in these fields In particular the section Disorders of Nervous Function has been expanded and descriptions of the common psychiatric disorders have been added After considerable discussion we concluded that the internist would find useful a consideration of these subjects as approached from the broad medical viewpoint An attempt has been made also to integrate psychiatric with neurologic concepts Brief discussions of the newer drugs which have proved valuable in the management of psychiatric disorders are included Part Three Biologic Considerations includes topics which were considered under the heading Physiologic Considerations in the first edition as well as a number of additional topics

The organization of the remainder of the book is similar to that followed in the second edition except that the Part dealing with the Care of the Patient has been placed at the end of the volume Following that Part tables of normal values are found in the Appendix

In the Parts which deal with specific disorders extensive revision has been carried out and many chapters have been *entirely rewritten Thus the* chapter Diseases of the Liver has been rewritten completely and expanded *In addition a Section* has been added which deals with Infections of Specific Tissues and Anatomic Sites *The discussions* of bacterial endocarditis and of pyelonephritis have been revised and appear in this Section rather than in the portions dealing with disorders of organ systems

The entire section on Diseases of the Nervous System has been rewritten in an attempt to view these disorders from the standpoint of problems they present to the physician rather than as specific entities only

Dr Victor McKusick has contributed the new chapter Heritable Disorders of Connective Tissue Since disorders on the skin are in many instances intimately related to internal diseases a brief discussion of the more pertinent aspects of dermatology by Dr Donald Pillsbury has been added The limitations of space prevented a more detailed discussion of this important subject

The many decisions concerning arrangement authors omissions condensations and new chapters were reached after prolonged group discussions During these complete frankness prevailed in criticizing the ideas and writings of our authors and of ourselves Each of us needed on many occasions to think of the banished duke and say to himself

This is no flattery—these are counsellors
That feelingly persuade me what I am

Once again we wish to express appreciation to our authors for their kindly forbearance with our frequent suggestions and criticisms Many of our authors were also most helpful as critics and in this respect we are especially indebted to Dr George Wright Likewise various other friends and colleagues read and criticized our own and other chapters Among these are Drs Samuel P Asper David Grob John E Howard and Kenneth Zierler of Baltimore Drs Stanley Cobb Mandel Cohen and Erich Lindemann of Boston Drs Franklin H Epstein Allan V N Goodyer and William Allan Tisdale of New Haven Drs Eugene A Bliss Jerome

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Color Plates

dyspnea for dyspnea is not outstanding in shock or in patients with pericardial adhesions and marked diminution of the cardiac output No cardiac asthma appears in advanced mitral lesions with a small cardiac output The disturbance of respiration induced by acidosis (Kussmaul breathing) differs from the dyspnea of cardiac patients Moreover some patients with cardiac asthma have a normal cardiac output Abnormal acids are conceded to act on the centers only in terminal stages for true hypoxemia and carbon dioxide excess do exist at this time In right heart failure (tricuspid insufficiency mitral stenosis) there is marked peripheral venous stasis with reduction of oxygen tension an increase of carbon dioxide tension and increased lactic acid content of the blood but no dyspnea of the paroxysmal nocturnal type

The Reflex Theory Most recent observers believe that attacks of cardiac asthma and pulmonary edema derive mainly if not wholly from reflexes originating in the lung and released by the pulmonary congestion This causes dyspnea in the manner discussed earlier Reflexes from these receptors may alter the excitability of the respiratory centers and make them more sensitive to carbon dioxide the physiologic stimulus of respiration

Reasons for the Nocturnal Appearance of Attacks

It has always been and still is difficult to explain the predominantly nocturnal appearance of paroxysmal cardiac asthma and pulmonary edema At present no satisfactory integration of the known facts seems possible It is hard to understand why physical effort in many cardiac patients with left ventricular failure with the consequent augmented strain on the left ventricle with the formation of non volatile acids in the blood and with increased pulmonary congestion as well does not elicit the attacks A few factors which may influence the nocturnal appearance of the attacks merit mention

1 Even under normal conditions the tonus of the parasympathetic nervous system increases decidedly during sleep and the influence of vagal tonus and of vagal reflexes on the occurrence of dyspnea is well established The fact that attacks of ordinary bronchial asthma develop more commonly at night is explained on this basis Similarly the greater incidence of gallbladder and renal colic of spasms and tenesmus at night and also the frequent onset of labor pains at this time have been explained by this increase in vagal tone

2 During sleep the carbon dioxide tension in blood and tissues mounts even in healthy people although only to a slight degree This fact is explained by the change in irritability of the respiratory centers which occurs in the absence of peripheral and cortical stimuli The special significance of carbon dioxide as a stimulus of the respiratory centers is universally accepted This physiologic nocturnal accumulation of carbon dioxide is superimposed upon the pathologic conditions prevailing in the centers although either factor alone constitutes only a weak stimulus in combination they may suffice to provoke an attack of dyspnea

3 During the day higher cortical areas continuously influence the respiratory centers promoting depressing or modifying their activity Respiration can be altered voluntarily and mental excitement as well as things seen heard or felt influence its rate and depth All these predominantly stimulating influences are absent at night When respiratory centers are left to themselves they may permit the development of local changes which would be instantly corrected during the day by increased respiration The diminished irritability of the centers during sleep permits the lungs to become more congested

4 Normally such circulatory values as the pulse rate and blood pressure fall at night and accentuate any slowing of circulation already present (Kroetz)

5 Tissue fluids pass into the blood at night (Brunn) a factor which is considered responsible for the nocturia of patients with heart failure The plasma volume increases because of the absorption of latent edema Recurrent attacks of pulmonary edema vanish without any other therapy if the patient receives a mercurial diuretic on the contrary pulmonary edema recurs when fluid is retained and reaches a certain level Furthermore the importance of water retention is emphasized by the frequent precipitation of attacks of pulmonary edema by the ingestion of large amounts of fluid

6 Rest in bed promotes the return of blood from the lower part of the body and other things being equal tends to accentuate pulmonary congestion in patients with left ventricular failure Sudden movements in bed or the transient hyperpnea during an exciting dream can increase the influx of blood from stagnant areas and thus augment pulmonary congestion

The disappearance of attacks without medical intervention is much more difficult to explain If the attack is attributed to the effect of abnormal stimuli on the centers or chemoreceptors blowing off of carbon dioxide and inhalation of larger amounts of oxygen would serve as an explanation The end of the attack is incomprehensible if it is provoked exclusively by pulmonary congestion and reflexes Overactivity of the sympathetic nerves or an increased output of pressor amines which cause the pallor and sweating of the patient and which is at least in part the reason for the hypertension during the attack may be responsible

The beneficial effect of morphine is readily explained on the basis of all theories which concede primary importance to the condition of the nerve centers or reflexes

Differential Diagnosis between Cardiac and Bronchial Asthma

The differentiation of cardiac from bronchial asthma is a difficult problem and one of great practical importance Not only is the prognosis of these two conditions vastly different but treatment is based on the distinction While epinephrine is usually valuable in an attack of bronchial asthma it is contraindicated in cardiac asthma On the other hand the specific therapeutic agent for cardiac asthma morphine is dangerous in bronchial asthma Accordingly a distinction between the two disorders is of paramount importance in an acute

attack although making such a distinction sometimes meets with unsurmountable obstacles

A carefully obtained history often but not invariably helps in the differentiation It may be devoid of value or unobtainable if the patient is seen during his first attack

Reference was made earlier to the fact that cardiac asthma may strike unexpectedly and without previous warning If careful interrogation reveals that the patient has no complaints referable to the heart or if an examination during the attack fails to disclose any distinct evidence of cardiac damage the differential diagnosis may be impossible during the seizure

Satisfactory examination of the heart during either kind of attack may be difficult Accurate percussion is impossible owing to the acute dilatation of the lung or chronic emphysema The emphysema the rales and the inability of the patient to hold his breath render auscultation difficult In both conditions the electrocardiogram may show only slight changes and usually it is not immediately available Often expiratory dyspnea is equally pronounced in both types of asthma As a rule the blood pressure is elevated during an attack of cardiac asthma whereas with bronchial asthma the blood pressure is generally low however hypoxemia may cause the blood pressure to rise in an attack of bronchial asthma so that it is improper to establish the diagnosis on this sign alone While it is a good rule to suspect cardiac asthma if the first attack develops in a patient of more than sixty years bronchial asthma may also develop at this age cardiac asthma may occur of course in much younger individuals Not rarely particularly in elderly individuals pulmonary and circulatory causes for dyspnea coexist and both forms of asthma may appear In such cases it becomes difficult to evaluate the mechanism of an attack

Examination after an attack subsides usually provides more information *to establish the diagnosis Nevertheless it must not be forgotten that* many lesions associated with cardiac asthma do not produce murmurs or cardiac enlargement and that patients may have an eosinophilia in the peripheral blood following an attack of cardiac asthma Therefore mistakes in both directions are common Sometimes prolonged observation is necessary before a decision is possible In these cases the determination of the circulation time may be *helpful* since it is normal in bronchial asthma and prolonged in most cases of cardiac asthma

Bronchospasm with asthmatic attacks occurs in patients with acute or chronic pulmonary congestion and such seizures are explained by a reflex spasm released from the congested vessels This thesis is supported by the immediate improvement following an intravenous injection of aminophylline in these patients Bronchial asthma may be a serious complication in the course of cardiac decompensation particularly in patients having coronary thrombosis with infarction and pulmonary congestion *In a series of 250* cases of cardiac asthma an allergic asthma coexisted in five (Palmer and White) Treatment without epinephrine was difficult and all succumbed Sometimes epinephrine must be given to patients suffering from both cardiac and bronchial asthma despite

the associated cardiac hazard This is permissible however only when the administration of aminophylline in large doses has failed to relieve the attack In general aminophylline is the remedy of choice for all patients with asthma when the differential diagnosis is not immediately possible

Pulmonary Edema

The clinical picture of pulmonary edema in left ventricular failure and its close relation to cardiac asthma has been described above

Pulmonary edema is not an entity Apart from the type resulting from left ventricular failure there are other varieties which deserve brief consideration

The Types of Pulmonary Edema (1) Pulmonary edema is observed in lesions of the nervous system as exemplified by skull fractures injuries of the cervical spine encephalitis brain tumors intracranial (subarachnoid) hemorrhage embolism and meningitis The permeability of the pulmonary capillaries has been said to be subject to central regulation In pulmonary edema of neurogenic origin produced experimentally changes of the blood pressure and other disturbances of cardiodynamics may be responsible It is of interest that veratrine given intravenously in minimal amounts to rabbits causes no effect When the same substance is injected suboccipitally pulmonary edema appears within a few minutes (Jarisch et al)

2 In coronary thrombosis pulmonary edema may develop suddenly irrespective of antecedent anginal pain Its appearance has been attributed to reflexes (Luisada)

In patients with myocardial infarctions we observed attacks of pulmonary edema occurring on the slightest provocation such as excitement or exertion but more often spontaneously at night without any apparent reason These attacks may occur over a period of many months even after patients resumed their work They appear without changes in the electrocardiogram or any sign on physical examination indicating new infarctions They appear sometimes nightly at the same hour They are observed without roentgenologic evidence of pulmonary congestion and cardiac enlargement They disappear suddenly

3 Pulmonary edema may develop at the beginning of a pneumonia or other inflammatory process in the lungs such as bronchitis particularly in elderly subjects and in those with pulmonary congestion The release of histamine from the affected tissue and the altered permeability of the vascular endothelium and alveolar wall explain this form

4 Pulmonary edema resulting from the gases used in chemical warfare is well known Thus one or two deep breaths of a concentrated sample of phosgene may produce a lethal pulmonary edema The symptoms appear after a latent period which may last nine hours Here too changes in permeability of the vascular endothelium and the release of histamine in the tissues are considered responsible for the appearance of this kind of pulmonary edema The [illegible]on of acids in the tissues hydrochloric acid from phosgene or nitric a[illegible] fumes may play a role

5 A very interesting form of pulmonary edema though fortunately rare may be encountered in certain cases of mitral stenosis in the absence of atrial fibrillation marked enlargement of the left atrium evidence of right heart failure or passive congestion in the liver If the congestion increases as the result of excitement or exertion and the intracapillary hydrostatic pressure exceeds the oncotic pressure of the plasma proteins pulmonary edema develops

It is easy to distinguish this form from the ordinary form of pulmonary edema of left ventricular failure These patients (usually women) develop one or more attacks daily during ward rounds while in the hospital or in the course of an animated conversation or walking a short distance on level ground or during sexual intercourse Presumably the propulsion of large volumes of blood into the lesser circuit which accompanies the acceleration of the heart rate in such cases increases pulmonary engorgement (pulmonary capillary pressure) sufficiently for edema to appear If the right ventricle functions well and the stenosis of the mitral valve is advanced the pulmonary congestion is extreme These patients must always have morphine available and sometimes it must be administered *prophylactically so that an examination may proceed without an attack* With longer duration of pulmonary congestion in mitral stenosis the attacks of pulmonary edema disappear Increasing sclerosis of the pulmonary vessels and fibrosis of the lungs make transudation of plasma impossible even if pulmonary congestion increases Thus this form of pulmonary edema is seen only under certain conditions in patients with mitral stenosis which is not too advanced It will be discussed in Chapter 12 in the section on this valvular lesion

The form of pulmonary edema which appears postpartum in patients with mitral stenosis is exceedingly dramatic Often the valvular lesion is so mild that the patient and family are unaware of its existence Since fatalities are not uncommon and are often unanticipated this catastrophe will never be forgotten by *anyone who has witnessed it The sudden return* of large amounts of blood from the pelvic veins to the heart and lungs seems to be responsible for the attack In this type of pulmonary edema the importance of increased intracapillary pressure as an initiating factor is evident

6 Pulmonary edema with hemorrhagic sputum may be noted during attacks of paroxysmal tachycardia We have seen them recur with every paroxysm in otherwise healthy persons This form cannot be easily explained by pulmonary congestion since the tachycardia affects the right and left ventricle equally and pulmonary congestion does not develop in these cases The patient exhibits only venous congestion and enlargement of the liver (inflow stasis) owing to the shortening of diastole Some experimental results show however that an abnormal spread of the excitation wave *during paroxysmal tachycardia may* alter contractility of one ventricle more than that of the other (Wiggers)

7 Following the administration of large quantities of fluid (saline glucose solutions) as recommended after operation in certain cases pulmonary edema is not rare Vagotomy with forcing of fluids is a well known experimental method for eliciting pulmonary edema in animals We have seen this variety (sometimes

combined with cerebral edema) following large transfusions postoperatively particularly in patients with hyperthyroidism. Fortunately warnings have been sounded against the abuse of forcing fluids intravenously particularly in patients with cardiovascular disorders.

8. Sometimes pulmonary edema may appear following thoracocentesis and the removal of large amounts of fluid. This form has been called edema ex vacuo. When the pressure on the pulmonary vessels is suddenly released a reactive hyperemia with copious transudation may cause inundation of the lung.

9. In pheochromocytoma an acute pulmonary edema during a hypertensive crisis may be the first sign of the disease. Sometimes it is lethal.

10. Pulmonary edema may appear as a manifestation of pulmonary embolism.

11. Often overlooked is the acute or chronic pulmonary edema in acute nephritis. The edema seen in azotemia is usually and perhaps invariably caused by heart failure. Many patients with pure azotemia do not exhibit pulmonary edema.

12. Pulmonary edema appears occasionally after the injection of the contrast medium for angiocardiography.

13. Finally terminal pulmonary edema must be mentioned. It occurs in the last minutes or hours of life in connection with a host of diseases.

Acute and Chronic Forms of Pulmonary Edema. In many cases of acute pulmonary edema the onset of symptoms is abrupt. Fluid fills the lungs in a few minutes and the patient practically drowns from the copious collection of serous fluid in the air passages. Sometimes subacute pulmonary edema exists. It is heralded by cough which gradually increases in intensity and profuse sweating. Early examination of the lungs reveals ominous crackling rales. In chronic pulmonary edema severe dyspnea moist rales and rose colored sputum may exist for many days.

Roentgenologic examination is invaluable in the diagnosis of the chronic or subacute types of pulmonary edema. The lung fields diffusely darken and cloudlike shadows appear. While the roentgenologic signs are more accentuated at the site of a pleural adhesion in pulmonary congestion (this holds for the clinical signs as well) the lung fields near an adhesion are much clearer in the case of pulmonary edema (Zdansky). If the pulmonary edema is localized often no evidence of congestion is found in the nonedematous areas. This indicates that congestion is not necessarily a precursor of pulmonary edema. In the chronic forms the edema may be limited to the central (circumhilar) area and therefore escapes discovery on physical examination (figure 1). Often it is more pronounced in the interstitial spaces rather than free in the alveoli and therefore also tends to elude detection by auscultation. In this form there are no symptoms. Pleural effusions are common in the chronic type.

Pulmonary edema may be found in only *one* lobe. The apices the bases near the diaphragm and also a small peripheral area near the chest wall often are free from opacities. Small shadows or dense circumscribed cloudlike shadows cannot easily be differentiated from primary or metastatic carcinoma or from pneumonia

(figure 2) In uremia a similar distribution of edema occurs when cardiac failure supervenes. Also typical is the interstitial edema with the butterfly pattern spreading in all directions from the hilus

Figure 1 shows the typical edema of a patient with hypertension without azotemia. The left ventricle is enlarged a butterfly pattern exists while the



Fig 1 Chronic pulmonary edema with typical hilar butterfly pattern. The patient suffered from hypertension without azotemia

peripheral parts of the lungs particularly the apices and bases are clear. Figure 2 shows dense shadows imitating pulmonary metastases

Mechanism A slow transudation of fluid takes place normally in the lungs. This fluid is however evaporated during aeration. In pulmonary edema increased permeability of the vascular endothelium must be assumed (Drinker) as the *protein content* of the edema fluid is great (2—4 per cent)

The importance of an increase of the fluid content of the lungs in the appearance of pulmonary edema has been stressed earlier. Equally important is the permeability of the vessels and perhaps also of the alveolar wall. If pulmonary congestion is rather acute the lungs are moist and much fluid exudes when they are sectioned at necropsy. The brown indurated lungs present in the chronic congestion of mitral stenosis are, however, dry. This is readily explained by the



FIG [illegible] Pulmonary edema with dense shadows in the right and left lung in a 22 year old patient with chronic nephritis without *azotemia*

progressive pulmonary fibrosis associated with the secondary sclerosis of the vessels of the lesser circuit; this makes transudation of fluid impossible despite marked congestion. It also explains why pulmonary edema and hemoptysis occur in early but not in late stages of mitral stenosis. Anoxia widens the capillaries locally and increases their permeability.

Consequences Profuse pulmonary edema may secondarily influence the circulation and the condition of the patient in other ways. Transudation of large volumes of serum into the lungs may cause dehydration since the amount of fluid lost in this way may be enormous. In the pulmonary edema of phosgene poisoning the weight of one lung may exceed 1 250 grams, that is, more than five times the normal weight. It has been estimated that as much as one half the plasma volume ma

be lost in extreme cases this causes the red blood cell count and hemoglobin to rise the blood nonprotein nitrogen to increase and a general acidosis to develop in the same way as after a severe burn of the body surface The mechanical obstruction of the air passages by edema fluid may cause asphyxia

In some attacks the blood pressure falls the pulse becomes thready respiration gasping and shock appears during which the patient expires

If the reflex tachypnea in a patient with pulmonary edema (and even in cardiac asthma) assumes a rapid and shallow character the tidal air may be reduced to 250 cc or even less Since about 150 cc are needed to fill the dead space gas exchange in the lung suffers Hypoxia may ensue in a few minutes resulting in even more rapid and shallow breathing During such tachypnea the oxygen unsaturation of the blood may amount to 40–50 per cent Accordingly changed arterial oxygen saturation may be the result rather than the cause of dyspnea

Hyperventilation may reduce carbon dioxide tension of the blood (hypocapnia) causing a shocklike syndrome with symptoms of tetany This dyspnea fails to serve any useful purpose and imposes a heavy burden on a heart already strained Moreover it increases the oxygen consumption of the body which is greater from the start owing to the high metabolic rate of cardiac patients

Functional Disturbances of Other Vegetative Centers in Paroxysmal Dyspnea

As with patients with Cheyne Stokes respiration those persons who suffer from cardiac asthma or pulmonary edema may exhibit a series of other respiratory phenomena These disturbances are also prone to occur at night and may be coincident with or independent of the paroxysmal episodes

An early sign of left ventricular failure is nocturnal cough While it represents a typical complaint in pulmonary congestion sometimes it develops in patients with progressive left heart failure before pulmonary congestion can be detected clinically It causes considerable discomfort and is often treated for a long time with cough medicines before its true nature is recognized The administration of digitalis usually abolishes it in a short while

Persistent sighing and yawning are frequently noted in patients with left ventricular failure Patients rarely complain about these symptoms but they are readily discovered Like the cough these phenomena vanish after a short course of digitalis therapy Since the yawning and sighing observed after an acute profuse hemorrhage are generally attributed to cerebral anemia that is to a diminished blood supply to the cerebral centers it is conceivable that a lessened cardiac output and slow peripheral circulation have a similar effect

The various respiratory phenomena just mentioned make patients with left ventricular failure extremely restless and noisy During ward rounds the physician often becomes aware of such a patient even when he is some distance away

Naturally left ventricular failure would never be diagnosed on the basis of these symptoms alone because other factors are more commonly responsible for

their appearance. They are mentioned merely to emphasize that vegetative centers in the neighborhood of the respiratory centers also function abnormally in left ventricular failure.

Concluding Remarks

The available evidence indicates that no single factor is exclusively responsible for attacks of paroxysmal nocturnal dyspnea. The various mechanisms and the interaction of multiple factors may explain why the character of the individual attacks varies. Thus the amount of fluid in the pulmonary parenchyma, the increased intracapillary pressure, the permeability of the pulmonary capillaries and of the alveolar epithelium subject to central regulation as well as to local changes may explain the presence or absence of pulmonary edema during an attack of cardiac asthma. Certainly the importance of reflexes on respiration has been grossly underestimated in the past, a mistake partly understandable since some of these reflexes have been discovered only recently. On the other hand an accreditation of the significance of these reflexes should not relegate the local situation in the lungs and the chemical regulation of respiration to a minor position.

Paroxysmal dyspnea may appear early in heart failure when cardiac dilatation and evidence of congestive failure is absent. Patients with hypertension *of [illegible] etiology and those with coronary sclerosis may have such an attack as the [illegible]* alarm. Just as peripheral edema is no index of the degree of cardiac fa[illegible] frequency and severity of paroxysmal nocturnal dyspnea affords [illegible] conclusion as to the extent of myocardial damage.

It is not clear why failure of the left ventricle alone causes par[illegible] turnal dyspnea, one might anticipate that all types of failure would [illegible] discrepancy presents great difficulties to those who believe that the [illegible] released exclusively by reflexes set in action by pulmonary con[illegible] congestion is certainly very marked in mitral stenosis and yet the [illegible] absent even in button hole mitral stenosis with an almost impr[illegible] and a marked reduction of minute volume. In the recent literat[illegible] stenosis attacks of paroxysmal dyspnea are said to appear frequ[illegible] lesion but we shall see in the section devoted to this valvular dis[illegible] not the case. The attacks also fail to appear in right ventricular fa[illegible] ple in severe tricuspid lesions under these circumstances pulm[illegible] may be negligible although the minute output of the heart is [illegible] peripheral circulation remarkably slow.

Cardiac asthma may disappear when right heart failure sup[illegible] recur if the latter is successfully treated.

Presumably the different factors discussed in the preceding [illegible] pulmonary congestion with its direct mechanical and reflex eff[illegible] chemical status of the centers and of chemoreceptors participa[illegible] of paroxysmal nocturnal dyspnea observed in left ventricular fa[illegible]

CHEYNE STOKES RESPIRATION

Fully developed Cheyne Stokes respiration with continual alternation of apnea and dyspnea is easily discovered when the apnea is prolonged and marked hyperpnea characterizes the dyspneic period Cheyne Stokes respiration is however often overlooked although it is one of the most constant and early signs of left ventricular failure During the examination it may exist in a fragmentary form and may be discernible only if looked for

Clinical Picture

In the consulting room and at home patients often fail to exhibit periodic breathing despite a thorough examination since the least excitement or physical exertion may abolish it If the patient can be induced to relax or to rest with closed eyes in a quiet room for only a few minutes periodic breathing may soon appear Sometimes there is no alternation of breathing and periods of apnea but a mere change from deep to more superficial breathing All gradations from a slight waxing and waning of the respiratory excursions to fully developed Cheyne Stokes can occur

Figure 3 was obtained from a patient fifty eight years of age who suffered from coronary sclerosis The upper tracing shows the periodic change from superficial to deep respiration The lower tracing was obtained a few minutes later when the patient relaxed and became more accustomed to the use of the spirometer dyspnea and apnea alternate In this tracing the lever moves downward with *inspiration*

Figure 4 shows a spirogram obtained from the abdomen (upper tracing) and chest (lower tracing) of a patient with hypertension and left ventricular failure In this tracing inspiratory movements are directed upward Whereas the apneic periods are short in figure 3 the dyspneic and apneic periods are almost equal in figure 4 The former situation seems more common Each phase may last as long as 50 seconds

The characteristic gradual increase of amplitude and the tendency of the chest to assume the *inspiratory position in the crescendo phase* are visible in both figures This accounts for the slow rise of the curve in the dyspneic phase (depression in figure 3) and the gradual reversion to the normal position in the descrescendo phase before the dyspnea begins Apnea usually occurs in the expiratory position In a given case the number of respiratory movements in each phase may remain constant for a long time

In addition to the periodic changes of respiration various other signs may be observed in patients with Cheyne Stokes breathing They likewise come and go periodically and are bound to a certain phase of respiration Thus the pupils may contract at the onset of apnea the blood pressure may increase in the dyspneic phase and arrhythmias such as extrasystoles and paroxysmal ventricular tachycardias may appear periodically Bradycardia may be noted in the apneic phase and tachycardia in the dyspneic phase the opposite situation may also

FIG 3 Cheyne Stokes respiration in a patient with coronary sclerosis

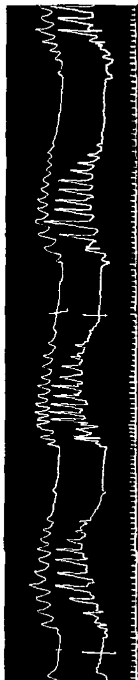


FIG 4 Cheyne Stokes respiration The upper tracing was obtained from the abdomen the lower from the thorax

prevail No fixed rules have been discovered for the appearance of most of these changes in one or the other phase of respiration Somewhat more constant is cough or deep sighing which may develop regularly during the crescendo phase of the dyspneic period

The patient s behavior may change with the different periods In well marked Cheyne Stokes breathing restlessness and involuntary movements of the limbs with twitching and clonic convulsions may be noted during dyspnea whereas the patient is fully relaxed with the eyeballs turned up as in coma during the apneic period Clouding of consciousness is not rare during apnea Delusions of persecution or a syndrome resembling amentia may occur and require commitment to a special institution

Periodic breathing is a normal phenomenon in infants (especially premature ones) during sleep in healthy elderly people and in normal subjects at high altitudes It is also observed in animals during hibernation Patients with sclerosis of the cerebral arteries frequently exhibit it Left ventricular failure is its most common cause Periodic breathing is conspicuously absent in patients with mitral or tricuspid lesions and in those with pulmonary disease and cor pulmonale

The assumption that Cheyne Stokes breathing is an ominous sign is often true however a very pronounced form may occur transiently in patients with coronary sclerosis and myocardial infarction until the left ventricle regains its strength If this happens the patient may remain free from respiratory embarrassment and other symptoms for many years Therefore the prognosis depends upon the underlying etiology rather than on the mere presence of the phenomenon

The absence of Cheyne Stokes breathing during the examination and despite a special search does not preclude episodes of nocturnal periodic breathing with extreme hyperpnea and when it is present during the day it tends to be more severe at night

The periods of hyperpnea may be associated with extreme anxiety and air hunger so that the patient cannot rest He suddenly sits up looks around in despair and utilizes all *auxiliary muscles for breathing In a few seconds* he relaxes lies down quiet or unconscious in apnea only to have the cycle repeated in a short time This situation may persist for hours and recur night after night When the attacks are milder the patient may leave his bed and restlessly pace the floor

Some patients with Cheyne Stokes breathing do not complain of dyspnea and deny any breathlessness despite the existence of long apneic periods These patients do however suffer from insomnia usually the result of the restlessness which to them is incomprehensible Accordingly many mention only the insomnia the actual cause of which is overlooked If examination fails to disclose Cheyne Stokes respiration careful interrogation of the attendants or relatives and sometimes even of the patient may reveal the presence of rhythmic changes in the depth of respiration

The possible existence of Cheyne Stokes respiration must be considered in every case of nocturnal dyspnea and every effort should be made to establish the diagnosis for this permits the introduction of effective specific treatment which speedily abolishes otherwise intractable complaints The therapy is discussed in the final chapter

Pathogenesis

No explanation for the pathogenesis of periodic breathing is entirely satisfactory All theories assume a changed excitability of the respiratory centers Slow circulation and local vascular disturbances (which provoke Cheyne Stokes breathing in cerebral vascular sclerosis and increased spinal fluid pressure) might produce hypoxia The apnea induced by depression of the centers is assumed to allow the accumulation of carbon dioxide and perhaps of nonvolatile acids which excite dyspnea when a certain threshold is reached During the dyspneic period carbon dioxide is removed from the blood and the hypoxia disappears Since the elimination of carbon dioxide removes the strongest stimulus for the respiratory center apnea returns

This conception leaves much unexplained While the mechanism of the fully developed Cheyne Stokes breathing becomes clear its beginning remains obscure Sometimes the apneic periods are very long while the dyspneic periods are exceedingly short in fact the periods of dyspnea may be so short that they can scarcely permit the elimination of accumulated metabolites Pryor as well as Gilmore and Kopelman are of the opinion that the prolongation of the circulation time in patients with Cheyne Stokes breathing is of primary importance Delayed passage of blood from the lungs to the arterial chemoreceptors and the respiratory centers permits an overventilation irrespective of the cause to last longer Therefore apnea must follow which in turn must be followed by dyspnea

In dogs Cheyne Stokes breathing could be produced by insertion of a delay system between heart and brain (Guyton et al) Normally with physiologic changes of respiration the oxygen and carbon dioxide content of the blood changes this altered blood reaches the respiratory centers quickly and regulation sets in When the circulation time of the blood is delayed the respiratory centers are reached after a longer interval This permits marked changes of the blood gas concentration to develop which as soon as they reach the centers provoke great changes of the respiration

The importance of hypoxia in Cheyne Stokes breathing is shown by the fact that periodic respiration may be induced in normal subjects if they breathe an oxygen poor mixture Moreover the Cheyne Stokes respiration of cardiac patients usually although not invariably disappears when oxygen is inhaled

The experience that Cheyne Stokes respiration may appear only during sleep or be aggravated then speaks in favor of cortical participation in its development This view has some experimental support (Schoen)

During Cheyne Stokes breathing the carbon dioxide tension must be low Hypoxia in combination with high carbon dioxide tension does not cause Cheyne

Stokes breathing Thus Cheyne Stokes respiration in a cardiac patient usually vanishes when a mixture containing 5 per cent carbon dioxide is inhaled and this may be the reason why patients with pulmonary emphysema practically never have this form of periodic breathing even when fully decompensated The reflex dyspnea of patients with mitral stenosis and pulmonary congestion prevents the appearance of Cheyne Stokes respiration

An objective survey of the medical literature discloses that most observers who deny the possibility that hypoxia in the respiratory center might play any part in the mechanism of other types of dyspnea readily concede its primary importance in Cheyne Stokes respiration This is somewhat paradoxic since Cheyne Stokes breathing often antedates other forms of dyspnea and appears in patients subject to recurrent attacks of cardiac asthma Cheyne Stokes breathing occasionally disappears as soon as sleep deepens perhaps because acidosis becomes greater (East)

The role played by a diminished blood supply to the centers in the genesis of Cheyne Stokes breathing is stressed by the following observation Otherwise healthy young individuals with paroxysmal tachycardia and a rapid ventricular rate may present Cheyne Stokes respiration for the duration of the tachycardia When the heart rate reverts to normal Cheyne Stokes respiration vanishes immediately The great reduction of the minute volume in such tachycardias is well known That the excitability of the respiratory centers is a determining factor for the appearance of Cheyne Stokes respiration is indicated by the periodic breathing of many young individuals after the administration of morphine

Periodic breathing resembling Cheyne Stokes respiration also occurs in patients with the Morgagni Stokes Adams syndrome when attacks follow each other at short intervals In this condition dyspnea follows cardiac standstill This is understandable since hypoxia and the accumulation of acid metabolites during the period of cardiac arrest may reach a point where they constitute an unusually strong stimulus for the respiratory centers and chemoreceptors Respiration ceases with the reappearance of the first pulse because hyperventilation during the period of cardiac standstill blows out large quantities of carbon dioxide from the blood in the lungs with the resumption of cardiac action after the standstill this acapnic blood reaches the respiratory centers and the stimulus for respiration is so weak that apnea results If the cardiac standstill recurs every few minutes as sometimes happens hyperpneic and apneic phases alternate so that the respiratory syndrome cannot be distinguished from ordinary Cheyne Stokes Usually the dyspneic phase coincides with cardiac standstill while the heart beats during the period of respiratory arrest

DYSPNEA IN CARDIAC NEUROSIS HYPERVENTILATION SYNDROME

A highly characteristic form of dyspnea is common in patients with nervous instability neurocirculatory asthenia anxiety neurosis and hysteria The breathing is typically irregular and sometimes accelerated so that it might be com

pared to the rapid irregular pulse of atrial fibrillation The continuous change of depth rate and level of respiration readily distinguishes it from other forms of dyspnea from the typical crescendo and diminuendo of Cheyne Stokes breathing from the slow respiration of increased intracranial pressure the transitory arrest of respiration without changes in depth (Biot type) and finally from the Kussmaul breathing of acidosis

Sometimes the respiration of patients with a cardiac neurosis resembles that seen in healthy subjects who on request breathe as fast as possible The same type of breathing may be noted in patients under the influence of some great emotional strain such as the unanticipated death of a close relative Dentists sometimes observe this type of dyspnea preceding an extraction or some other operation

Since rapid and superficial respirations may reduce the tidal air to 250 cc or less the volume of gases available is insufficient for a normal exchange Acute hypoxia thus results

Hyperventilation Syndrome In the hyperventilation syndrome faintness dizziness tingling of the fingers sense of impending death and even loss of consciousness may appear Patients may experience palpitation dysphagia anxiety tightness about the chest or a dull pain in the lower anterior chest wall Hyperventilation due to encephalitis or poisoning with salicylates may lead to the same syndrome (Lewis) These patients feel cold and clammy when touched

Peripheral and peri oral paresthesias appear related to respiratory alkalosis The low carbon dioxide content of the arterial blood leads to constriction of smaller vessels causing among other phenomena cerebral hypoxia Signs and symptoms of tetany appear

If the respiratory excursions increase but slightly in rate while their depth becomes greater larger quantities of carbon dioxide are blown off so that hypocapnia and alkalosis develops Want of carbon dioxide may cause the *larger* peripheral vessels including the veins to dilate so that larger amounts of blood are retained in the venous depots Consequently the amount of blood returned to the heart is reduced the pulse becomes small or even impalpable the blood pressure may fall the neck veins fill poorly and a shocklike syndrome may appear We have been repeatedly summoned to see patients who were supposed to have developed shock or circulatory failure following an operation but who exhibited only this syndrome

Individuals who present this type of respiration frequently suffer from sighing respiration as well The latter is discussed below

Holding the breath rebreathing into a paper bag or the inhalation of 5 per cent carbon dioxide help Treatment of a psychoneurosis is often necessary

Electrocardiographic changes during hyperventilation have been repeatedly described They are not due to alkalosis (Scherf and Schlachman)

DYSPNEA IN ENDOCRINE DISORDERS

Patients who have sighing respiration (suspirious respiration) often complain of dyspnea This does not apply to those who sigh deeply because of grief or

sorrow nor when a sigh is taken to relieve mental tension but it is true in another large group of patients with sighing respiration The patient usually a woman complains that the breath will not go through or that the breath goes only so far (pointing to the upper third of the sternum) or that she is unable to take a deep breath Great relief is secured once she succeeds in breathing deeply (the sigh) Sometimes the complaint of breathlessness is reported with considerable excitement and apprehension Patients are rarely aware that they are compelled to sigh periodically

Figure 5 reproduces a spirogram obtained during the determination of the basal metabolic rate of a 29 year old woman A deep sigh occurs after 3 to 5 normal respirations Apart from the deep sighs there is no irregularity in rate or

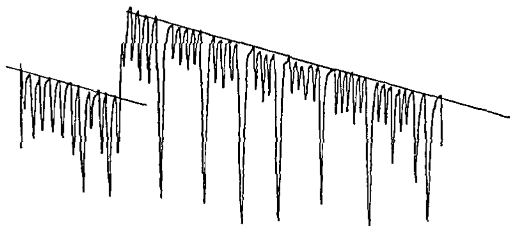


Fig 5 Sighing respiration

depth of respiration Sometimes the sigh may occur after every second or third respiration for a time or alternate with a normal respiratory excursion (respiratio alternans) Since the preceding as well as subsequent respirations are unchanged the deep breath is not compensatory

The deep sigh represents a maximal respiratory effort and corresponds closely to the vital capacity It will frequently be discovered if spirograms or basal metabolism tracings are inspected with this phenomenon in mind It is more pronounced in the recumbent position Christie found such sighs in 6 9 per cent of 1 500 consecutive respiratory tracings In 2000 successive spirograms investigated by one of us sighing respiration was found in 68 only two of these patients were males One of these men had undescended testes Thirty five of the females were beyond 35 years of age and had symptoms suggestive of disturbed ovarian function All but three of the other patients were listed as examples of hyper or hypothyroidism uterine fibroids functional disorders of the nervous system and endocrine imbalance

In the few investigations devoted to it sighing respiration has usually been considered a sign of neurosis and its great incidence in neurocirculatory asthenia

is stressed While patients with neurocirculatory asthenia often display this type of breathing it is a common and regular finding in women with hypo ovarianism It is observed in adolescents and it is particularly prominent at the climacterium even in women over 60 years of age awareness of its occurrence in these conditions will prevent serious diagnostic errors

Sighing respiration certainly does not result simply from estrogen deficiency for it appears in patients suffering from such other disorders as hyper and sometimes hypothyroidism and it is often absent after panhysterectomy It is interesting that the phenomenon is infrequent in males Presumably the endocrine imbalance which plays a dominating role in the production of other climacteric symptoms is responsible for sighing respiration in an unknown way

Sighing respiration is often rapidly abolished by therapy with estrogens The great apprehension and anxiety exhibited by many of those affected has led some observers to regard the symptoms as manifestations of hysteria but specific treatment creates a great change and the distress may vanish in a few days

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Chapter 2

The Size of the Normal Heart

THE AVERAGE WEIGHT of the adult heart is 250 grams (females) to 300 grams (males). There is a definite correlation between body weight and the weight of the heart although this correlation is not valid in obesity. The normal heart at birth weighs about 23 grams. The weight of the heart increases in proportion to the weight of the skeletal muscles (a fact known to Harvey). The taller and the heavier a man is, the larger his heart.

Generally speaking, the weight of the heart in man and animals increases with added physical activity. It is small in people engaged in sedentary work but large in athletes and in those who do heavy physical labor.

Position of the Diaphragm. The size and shape of the normal heart varies with the individual; it may even change in the same person within a short time, for it depends upon many factors. The position of the diaphragm, for example, is an influencing factor. A diaphragm too low to afford cardiac support results in a pendulum or vertical heart. The observer may consider such a heart normal in size even though an enlargement is actually present. If, on the other hand, the diaphragm is elevated, the apex beat may be located outside the mid-clavicular line and the mistaken diagnosis of cardiac enlargement may be made.

Figure 6 shows how the heart changes its size and shape when the position of the diaphragm varies. Figure 6a depicts the heart when the diaphragm is high. The heart seems large, with a pronounced waist line. The vascular band is wider and an enlargement of the aorta may be erroneously assumed. In Figure 6c (low diaphragm) the cardiac axis is perpendicular, causing the heart to appear small. Figure 6b shows the form of the average normal heart when the diaphragm *is in a normal position.*

Physical Exertion. After brief but heavy physical exertion the heart *may* temporarily enlarge, such enlargement lasting for only a few minutes. [illegible] subsequent reduction of size may persist for hours or days. The enlarg[illegible] probably due to increased venous return with greater cardiac fillin[illegible] *reduction in size can be attributed mainly to the tachycardia which* [illegible] *diastole (ventricular filling) and to an increase in sympathetic tonus.*

After prolonged exertion, cardiac enlargement may be mor[illegible] more marked; this is particularly apt to occur when the mus[illegible]

damaged the individual is unaccustomed to such effort and the exertion is unusually strenuous (Zdansky)

Heart Rate Cardiac rate exerts a marked influence on cardiac size The heart becomes smaller in tachycardias and larger during bradycardias Thus in cases of heart block or in healthy young athletes who develop bradycardia while in training the heart is large In these instances the augmented size is a result of prolonged diastole with greater ventricular filling

Blood Volume The heart becomes smaller after a copious phlebotomy and after diarrhea with dehydration and becomes larger for a few minutes after an intravenous infusion It is very small in patients with Addison s disease particularly during a crisis when there is reduction of blood volume it returns to normal when the crisis is treated successfully (McCormack)

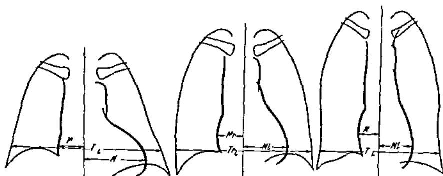


FIG 6 Changes in the shape of the normal heart and of the transverse cardiac diameter in different positions (a) With a high diaphragm (b) normal position of the diaphragm (c) with a low diaphragm (Zdansky)

Measurement Since so many factors exert a marked influence upon cardiac size methods of finding slight enlargement by mensuration of different diameters are fraught with error and may lead to false impressions Moreover such measurements do not permit an unequivocal detection of early cardiac enlargement and they are superfluous when definite changes are present therefore they will not be discussed in detail If measurements are recorded films ought to be obtained when the patient is recumbent since this position allows better filling and minimizes variations Tables have been constructed which predict the cardiac measurements for various heights and weights (Ungerleider) In many conditions e g deformities of the chest pregnancy or ascites mistakes will occur when these tables are used

The cardiothoracic ratio which enjoys considerable popularity is obtained in the following manner The width of the chest is measured at the level of the upper most portion of the diaphragmatic dome the inner side of the ribs being used as end points The transverse diameter of the heart is considered the sum of the greatest distances between the right and left cardiac borders from the midline (fig 6) The normal ratio between the diameter of the chest and the transverse diameter

of the heart varies with the age and size of the individual but it may be considered 2 1 for the adult male Figure 6 shows how these values depend upon the position of the diaphragm the ratio increases as the diaphragm descends Abnormal values are obtained in patients who are very tall or stocky The cardiothoracic ratio (or cardiopulmonic ratio) therefore furnishes little clinical help in determining early cardiac enlargement Moreover certain parts of the heart may be enlarged even when the transverse diameter is normal (see outflow tract of the right ventricle)

Congestive heart failure may be present with a small heart (in myocardial infarction) and it may be absent with the very large hearts of cor bovinum in hypertension or aortic insufficiency

In patients with scoliosis or funnel chest the heart is often displaced and appears larger than it actually is

That changes of shape often are of greater diagnostic value than changes of size will be evident from the discussion in the succeeding chapters

Tonus of the Heart This phenomenon defies definition We refer the reader to Zdansky s discussion of the problem Many authors believe that tonus is not a separate function of the heart but anyone who sees the flabby almost shapeless heart resting on the diaphragm in certain myocardial diseases and compares it with the heart of normals or of those in good physical condition will be inclined to think otherwise

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Chapter 3

Hypertrophy and Dilatation of Cardiac Chambers

General Discussion

Dilatation of a chamber of the heart often is an occurrence which enables the heart to adapt itself to a changed situation It appears under different conditions

First an increased inflow into the heart (arteriovenous fistula patent ductus arteriosus rapid intravenous infusions) augments cardiac filling and leads to an increased content of blood at the end of diastole As a consequence the myocardial fibers are subjected to greater stretch so that according to the law of Starling a stronger contraction results and the heart is able to cope with the increased demand The dilatation at the end of systole may be minimal This is also the manner in which the left ventricle disposes of increased filling if a mitral or aortic insufficiency is present Within physiological limits the larger the volume of the heart the greater is the energy of its contraction and the amount of chemical change at each contraction The energy of contraction however measured is a function of the length of the muscle fiber (Starling) In addition to the volume at the end of diastole hormonal and neurogenic factors also are influences on cardiac performance

Starling s law of the heart has been questioned lately but has also been confirmed and amplified (Sarnoff)

Second dilatation occurs when the heart works against increased resistance (hypertension aortic stenosis) and is incapable of expelling all of its contents at the end of systole Cardiac output initially diminished soon becomes normal

Third if a primary myocardial lesion or one caused by coronary artery disease renders the muscle unable to contract against the resistance of a normal diastolic blood pressure the amount of residual blood again increases Filling is greater and contraction improves

Hypertrophy develops within a few weeks in such hearts The increased stretch presumably acts as the physiologic stimulus In hypertrophy muscle fibers become larger in rare instances a numeric increase of fibers has been observed (Linzbach)

Hormonal factors in the development of hypertrophy are discussed by Raab

Atrial Hypertrophy and Dilatation

Physicians are often confused about the possibility of determining the presence of hypertrophy or dilatation of the atria or the ventricles by physical examination It may be worthwhile therefore to review the subject in a few introductory remarks

Atrial Hypertrophy

Hypertrophy of the right or left atrium even when extreme cannot be detected by physical examination moreover it does not significantly change the shape of the heart on x ray examination The slight dilatation that invariably precedes hypertrophy scarcely exceeds the limits of normal variation Therefore massive hypertrophy of the left atrium in mitral stenosis or of the right atrium in tricuspid stenosis cannot be diagnosed except by inference

Dilatation of the Left Atrium

This occurs in two ways both illustrated by the two lesions which commonly deform the mitral valve In mitral stenosis the atrium can compensate for some time by hypertrophy alone Only when hypertrophy no longer suffices and the atrium cannot expel its contents through the narrowed valve does the retention of larger amounts of residual blood at the end of systole cause dilatation This is called secondary dilatation From the onset of mitral insufficiency however blood enters the atrium both from the pulmonary veins and under high pressure from the left ventricle by *regurgitation causing a primary dilatation to appear* early

Dilatation of the left atrium may occur mainly along the left cardiac border where it straightens the waist line and causes dullness in the second interspace to the left of the sternal border this is one reason for mitralization of the heart Owing to this enlargement and also to the rotation of the heart to the left (clockwise) in mitral stenosis the left atrium may become visible on the right cardiac border during roentgenologic examination Normally it just reaches this border *In some patients with mitral insufficiency and a huge left atrium* a very strong pulsation appears at the *right* of the sternum between the fourth and sixth ribs for the atrium fills under high ventricular pressure and may closely approximate the chest wall in this area Marked enlargement of the left atrium may cause left paravertebral dullness between the third and sixth dorsal vertebra We have seen patients with a giant left atrium in whom the left pleura was tapped because of a mistaken diagnosis of pleural effusion

The position of the left atrium as the uppermost posterior part of the heart and *its location beneath the tracheal bifurcation in front of the esophagus* explains why it displaces these structures when it enlarges Compression of the left main bronchus and displacement of the esophagus occur these actions will be discussed in the chapter on mitral stenosis

Radiologic examination will best reveal dilatation of the left atrium in the early stage if the patient is placed in the right anterior oblique position i e turned 30 to 40 degrees to the left Then the normally clear retrocardiac space is filled by the shadow of the left atrium A study of the course of the esophagus in this position is helpful If the patient swallows a suspension of barium sulfate



FIG 7 Displacement of the esophagus by an enlarged left atrium in mitral stenosis (right anterior oblique position)

the normal esophagus is seen to swerve in a slight arc whose concavity is directed toward the abdomen In left atrial enlargement the esophagus is displaced sharply backward just beneath the bifurcation of the trachea

In figure 7 the typical displacement of the esophagus just beneath the bifurcation of the trachea is clearly visible The picture was obtained in the right anterior oblique position from a patient with rheumatic mitral stenosis and regurgitation

Occasionally a slight circumscribed displacement may occur without left atrial enlargement when the diaphragm is high Therefore the observation should be made during deep inspiration Persistent esophageal displacement in

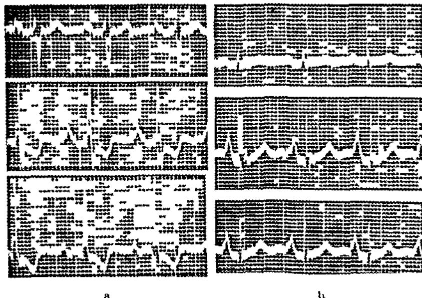
deep inspiration speaks in favor of enlargement of the left atrium A pericardial effusion or an enlargement of the left ventricle causes a similar dorsal displacement of the esophagus this however does not begin just below the bifurcation and is less sharply circumscribed

Dilatation of the Right Atrium

This can be easily demonstrated by percussion since dullness is obtained at the right lower cardiac border and to a variable extent beyond the edge of the lower sternum This enlargement is also readily demonstrated by x ray but it must be differentiated from displacement by an enlarged right (or even left) ventricle Usually such differentiation is possible when the patient is in the oblique position and when an examination is made of the neck veins and the liver Enlargement of the right atrium when extensive is accompanied by hepatomegaly and congestion of the neck veins

Electrocardiogram

The electrocardiogram offers some aid in the differentiation of atrial hypertrophy and dilatation In mitral disease with predominant left atrial dilatation



a b

Fig 8 The three standard leads Figure 8a shows a right ventricular strain pattern and widened slurred P waves in leads I and II in a patient with mitral stenosis figure 8b shows abnormally high P waves in leads II and III in a patient with chronic pulmonary emphysema

abnormally wide slurred and notched P waves appear in leads I and II (figure 8a) This is probably due to intra atrial conduction disturbances associated with marked left atrial dilatation In right atrial hypertrophy as seen in the various types of cor pulmonale the P waves are low in lead I but unusually high often

over 3 mm in leads II and III (figure 8b) These waves are not wide abnormally slurred or notched In this instance hypertrophy of the right atrium seems solely responsible The tall P waves (figure 8b) are followed by depressed P R and RS T segments This is due to the pronounced T waves of the P (Ta or Tp waves)

Very large P waves in all leads are often seen in congenital heart diseases such as the tetralogy of Fallot Occasionally these typical changes of the P waves provide diagnostic help in difficult cases Figure 9 shows the huge P waves in leads I and II obtained from a 4 year old child with tetralogy of Fallot

VENTRICLES

Inflow and Outflow Tracts

Cardiac dilatation and hypertrophy do not develop simultaneously in all parts of the right or left ventricle when these structures are subjected to increased strain The sequence of cardiac dilatation and hypertrophy follows certain rules (Kirch)

Each ventricle may be divided into two parts which function as physiologic units (figure 10) The inflow (receiving) portion is located between the atrio ventricular orifices and the apex while the outflow (expelling) portion is found between the apex and the semilunar valves These sections converge toward the apex The inflow tract of the right (or left) ventricle is represented by the posterior part of the ventricles and adjoining septum whereas the outflow tract is formed by the anterior ventricular wall and adjoining septum When dilatation (and hypertrophy) develop in a healthy right (or left) ventricle owing to an increased pressure in the lesser (or systemic) circulation the only part affected at first is that situated immediately below the semilunar valves (terminal portion of the outflow tract) The dilatation gradually extends toward the apex and only then affects the inflow tract as well Thus dilatation progresses gradually moving from one part to another in a direction opposite to that of blood flow If for some reason the cause of ventricular hypertrophy disappears (left ventricular hyper trophy in hypertension) recovery starts at the end of the inflow section and moves with the blood stream down toward the apex and then up to the arterial orifice This tonogenic dilatation the result of increased resistance causes the heart to enlarge mainly along the longitudinal axis of the outflow tract

These postmortem observations have been confirmed by experiments on the mammalian heart In aortic stenosis the conus area is exposed to increased intraventricular pressure for a longer time and it retains more residual blood than the rest of the ventricle at the end of systole With increasing resistance to the emptying due to an increasing residuum of blood the process gradually extends toward the apex this produces a gradual dilatation in a direction opposite to that of the intracardiac blood stream

In patients with mitral insufficiency the inflow of larger quantities of blood from the atrium to the left ventricle during diastole leads to an early dilatation

of the inflow tract the same process applies to the right ventricle in a tricuspid insufficiency These rules are not applicable to cardiac dilatation resulting from myocardial damage (myogenic dilatation) since here the entire chamber dilates simultaneously This is seen in myocarditis or coronary sclerosis

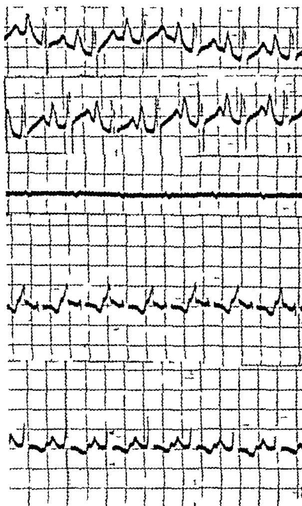


Fig 9 Huge T waves in the standard leads as well as in V2 and V5 in a child with Fallot's tetralogy

Involvement of the inflow or outflow tracts of the right ventricle can be recognized fluoroscopically especially in the left anterior oblique position Occasionally important diagnostic data are obtained by this means The inflow tracts of both ventricles are situated posteriorly the outflow tracts anteriorly Hence the most anterior portion of the heart is the outflow tract of the right ventricle (conus of the pulmonary artery) while the most dorsal section is the inflow tract of the left ventricle and the left atrium

In figure 10a b c the positions of the inflow and outflow tracts of the right and left ventricles are indicated by arrows Figure 10a is a postero anterior view Figure 10b shows the right anterior oblique position and figure 10c the left anterior oblique position

It can be seen in figure 10a that the inflow and outflow tracts of the *left ventricle* run almost parallel The *inflow tract from the mitral valve to the apex* is situated posteriorly and borders on the posterior mediastinum The outflow tract from the apex to the aortic orifice forms the left cardiac border Simple

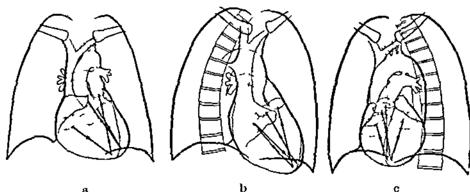


FIG 10 Course of the inflow and outflow tracts of the right and left ventricles (a) postero anterior position (b) right anterior (c) left anterior oblique position (Zdansky)

prolongation of the outflow and inflow tracts along their axes without dilatation along the transverse diameter will displace the apex beat downward but the heart will not appear larger as more of the left ventricle will be hidden in the abdominal shadow than under normal conditions

The inflow tract of the *right* ventricle extends from the tricuspid orifice toward the apex of the right ventricle lying more or less horizontally upon the diaphragm The outflow tract of the right ventricle on the other hand runs almost perpendicularly upward from the apex to the pulmonary orifice

Dilatation of the inflow tracts is best studied in the left anterior oblique position (figure 10c) for which the patient turns 40 to 60 degrees to the right If the inflow tract of the left ventricle is dilated a greater part of the left ventricle is hidden in the shadow of the vertebral column enlargement of the inflow tract of the right ventricle makes the right heart border more prominent so *that it bulges into the right lung field*

The enlargement of the outflow tract of the right ventricle is best studied in the right anterior oblique position (figure 10b) which brings the prominent conus into view in the postero anterior position it causes filling of the waist line

Hypertrophy of the Left Ventricle

One often hears the remark that the right or left ventricle is hypertrophied because of some particular finding on percussion or x ray examination It may not be amiss to stress that concentric hypertrophy *even if massive does not*

necessarily alter cardiac size enough for demonstration by percussion Only *one* sign of left ventricular hypertrophy is found on physical examination a heaving strong apical impulse which can scarcely be suppressed by the examining fingers despite the use of considerable force *Such a sign however is uncommon The apical impulse is not palpable in the recumbent patient in at least 60 per cent of normal adults This is to be expected since most of the left ventricle is located* posteriorly the apical area is thoroughly covered by lung and the impulse is absorbed by the chest wall Conditions are not much different when there is hypertrophy of the ventricle Accordingly the apical impulse is heaving only in a minority of cases When this sign is positive it often stems also from displacement of the apex by dilatation of the left ventricle bringing it nearer to the chest wall Hypertension or aortic stenosis may persist for years and hypertrophy of the left ventricle may reach great proportions without there being any evidence *from physical examination to prove the existence of this hypertrophy Usually the presence of hypertrophy is merely inferred its existence cannot be positively* demonstrated

The situation is somewhat similar on x ray examination Only greater rounding of the lower left cardiac border and apical area is found but this finding is also noted in normal hearts and in athletes In concentric hypertrophy of the left ventricle for a long time only the outflow tract — which is not very accessible to examination — is involved Hypertrophy of the left ventricle need not necessarily be accompanied by a similar change in the right ventricle

The electrocardiogram is discussed below

Hypertrophy of the Right Ventricle

Hypertrophy of the right ventricle can be demonstrated more readily The right ventricle lies anteriorly immediately behind that part of the thoracic wall called the precordium In this area the lung either does not cover the heart or covers it only in part and thus right ventricular hypertrophy causes a diffuse and increased pulsation of the whole area to the left of the lower sternum The most anterior part of the heart is the outflow tract of the right ventricle that is *the conus of this ventricle Since in the majority of cases it undergoes* hypertrophy first a pulsation of the conus area is palpable very early

It is in cases of pulmonary emphysema and abnormalities of the thoracic wall that the pulsation does not appear The sign is not pathognomonic however since it is found in the absence of right ventricular hypertrophy i e in the juvenile heart when the chest wall is thin and in the overactive heart of cardiac neurosis hyperthyroidism or avitaminosis (beriberi heart) The differential diagnosis is nevertheless usually easy

Pure hypertrophy of the right ventricle without dilatation is difficult to detect by x ray When the conus of the right ventricle is accentuated and the right ventricular contour is more prominent in the left anterior oblique position dilatation of considerable degree has already taken place

The electrocardiogram is discussed below

during systole if the amount of fluid in the alveoli is greater than normal (cardio pulmonic rales) In cases of right ventricular hypertrophy and dilatation a larger part of the heart is close to the anterior chest wall and the lung having lost its elasticity due to chronic congestion cannot expand with sufficient speed during cardiac systole Therefore the atmospheric pressure presses on the soft inter spaces and causes systolic retractions — which are so often misinterpreted as being caused by pericardial adhesions

Right ventricular dilatation usually involves the outflow tract primarily (tonogenic dilatation) the conus area therefore shows the first evidence of en largement The axis of the outflow tract of the right ventricle is almost perpen dicular (figure 10a) Upward dilatation develops easily whereas the diaphragm prevents downward expansion Therefore a prominent conus of the right ventricle in the right oblique position and mitralization in the postero anterior position are early roentgenologic signs of right ventricular dilatation The enlarged conus of the right ventricle is best visualized when the patient is standing in a lordotic position

Dilatation of the inflow tract of the right ventricle e g in a tricuspid regur gitation causes a marked enlargement of the cardiac shadow to the right and left since the axis of the inflow tract of the right ventricle runs almost horizon tally from right to left

Electrocardiogram

The electrocardiogram may be normal despite the presence of cardiac hyper trophy and dilatation In more advanced hypertrophy and dilatation of a ven tricle the electrocardiogram assumes a typical pattern The presence or absence of an axis deviation which was strongly emphasized a few years ago is of little importance In patients with left ventricular hypertrophy but a perpendicular cardiac axis no left axis deviation need be present while in right ventricular hypertrophy and a horizontal heart left axis deviation has been seen *Thus the position of the heart is of importance for the appearance of an axis deviation* If a marked emphysema supervenes in a patient with left ventricular hyper trophy due to hypertension and the heart assumes a more perpendicular position the two factors (hypertrophy and position) acting in opposite directions may cause the disappearance of any deviation or even the appearance of a right axis deviation In left ventricular hypertrophy occasionally the QRS complexes are 0 10 or 0 11 second wide The RS T segments and T waves are displaced in the standard leads in a direction opposite to the QRS complexes

The chest leads are of greater importance than the standard leads for the diagnosis of hypertrophy As figure 13 shows in left ventricular hypertrophy *the R wave in V2 may become lower or may disappear while the S wave is deeper The RS T segment is often more elevated than in normal hearts In V6 the R wave is very large the S wave is often absent and the RS T segment as well as the T waves are depressed below the zero line as in lead I* In right ventricular

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Dilatation of Left and Right Ventricle

Dilatation of the left or right ventricle increases the size of the heart and therefore cardiac enlargement is found on percussion or by x ray examination Since both ventricles are situated mainly in the left chest it is often impossible to decide by percussion alone which ventricle is enlarged

Left Ventricle The position of the apical impulse if present permits one to deduce which ventricle is dilated The normal apical impulse is located in the fifth left intercostal space within the mid clavicular line Dilatation of the left



FIG 11 Displacement of the apex beat with dilatation of the left (a) and of the right (b) ventricle

ventricle displaces the apex beat outward and *downward* in the direction of the arrow in figure 11a The left leaf of the diaphragm is often pushed downward When the outflow tract of the left ventricle dilates e g in hypertension or aortic valve stenosis the expansion occurs almost exclusively along the axis of the outflow tract (figure 10a) If there is no widening along the transverse diameters percussion and fluoroscopy will fail to disclose much cardiac enlargement in the usual sense The heart merely becomes oblong (egg shaped) and as pointed out before a greater part of the enlarged ventricle is hidden in the abdominal shadow This part becomes visible only if a large amount of gas is present in the colon or stomach

In myocardial lesions and in more advanced stages of left ventricular dilatation the inflow tract becomes involved the heart enlarges along the transverse axis and the characteristic aortic configuration appears

Right Ventricle With right ventricular dilatation the apex beat is displaced mainly outward but not downward (figure 11b) Often it is situated a little higher than the normal location and an epigastric pulsation is frequently present

Since the right ventricle is located anteriorly the occurrence of hypertrophy and dilatation of this chamber in childhood (before the chest develops fully) causes a *characteristic bulge of the precordium The left mammilla therefore may* have a different position than the right one

Figure 12 shows a characteristic bulge over the precordium in a patient who developed rheumatic mitral stenosis and regurgitation in early childhood Pronounced hypertrophy and dilatation of the right ventricle were present

Right ventricular dilatation may also cause a diffuse systolic retraction of the interspaces in the precordial area. Normally, when the ventricles contract, the



Fig 1 Bulge of the precordial area of the chest wall in a patient with a rheumatic mitral stenosis and regurgitation

negative intrathoracic pressure increases because blood leaves the chest; the elastic lung bordering on the heart immediately widens and fills the gap (Lang). This explains why moist rales are heard over the anterior part of

during systole if the amount of fluid in the alveoli is greater than normal (cardio pulmonic rales) In cases of right ventricular hypertrophy and dilatation a larger part of the heart is close to the anterior chest wall and the lung having lost its *elasticity due to chronic congestion cannot expand with sufficient speed during* cardiac systole Therefore the atmospheric pressure presses on the soft inter spaces and causes systolic retractions — which are so often misinterpreted as *being caused by pericardial adhesions*

Right ventricular dilatation usually involves the outflow tract primarily (tonogenic dilatation) the conus area therefore shows the first evidence of en largement *The axis of the outflow tract of the right ventricle is almost perpen* dicular (figure 10a) Upward dilatation develops easily whereas the diaphragm prevents downward expansion Therefore a prominent conus of the right ventricle *in the right oblique* position and nutralization *in the postero anterior position* are early roentgenologic signs of right ventricular dilatation The enlarged conus of the right ventricle is best visualized when the patient is standing in a lordotic *position*

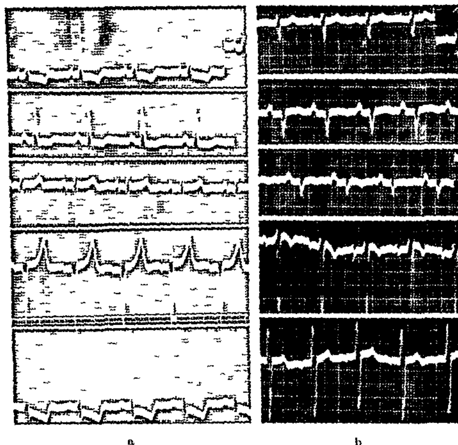
Dilatation of the inflow tract of the right ventricle e g in a tricuspid regur gitation causes a marked enlargement of the cardiac shadow to the right and *left* since the *axis of the inflow tract of the right ventricle runs almost horizon* tally from right to left

Electrocardiogram

The electrocardiogram may be normal despite the presence of cardiac hyper trophy and dilatation In more advanced hypertrophy and dilatation of a ven tricle the electrocardiogram assumes a typical pattern The presence or absence of an axis deviation which was strongly emphasized a few years ago is of little importance In patients with left ventricular hypertrophy but a perpendicular cardiac axis no left axis deviation need be present while in right ventricular hypertrophy and a horizontal heart left axis deviation has been seen Thus the position of the heart is of importance for the appearance of an axis deviation *If a marked emphysema supervenes in a patient with left ventricular hyper* trophy due to hypertension and the heart assumes a more perpendicular position the two factors (hypertrophy and position) acting in opposite directions may cause the disappearance *of any deviation or even the appearance of a right axis* deviation In left ventricular hypertrophy occasionally the QRS complexes are 0 10 or 0 11 second wide The PS T segments and T waves are displaced in the standard leads in a direction opposite to the QPS complexes

The chest leads are of greater importance than the standard leads for the diagnosis of hypertrophy As figure 13 shows in left ventricular hypertrophy the I wave in V 2 may become lower or may disappear while the S wave is deeper The RS T segment is often more elevated than in normal hearts In V5 the R wave is very large the S wave is often absent and the PS T segment as well as the T waves are depressed below the zero line as in lead I In right ventricular

hypertrophy the R wave in V2 is often but not invariably taller than usual and the T wave is flat or inverted In V5 there are deep S waves preceded by R waves of medium height The RS T segments and T waves are normal in V6



a b

Fig 13 Electrocardiograms showing the patterns of left (a) and right (b) ventricular hypertrophy Figure 13a was registered from a 68 year old woman with hypertension figure 13b was obtained from a 58 year old patient with pulmonary emphysema

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Chapter 4

Percussion and Auscultation

Percussion

Introduction

In recent years with the development and increased availability of roentgenology percussion of the cardiac borders is hardly taught or practiced in many institutions It has been called a dying method which served in the past but should be extruded from our important and growing number of clinical and laboratory methods (Parkinson) One must concede that roentgenology and especially fluoroscopy give more exact and more detailed information about the size and what is more important the shape of the heart Moreover patients with emphysema obesity or a deep or deformed thorax (kyphoscoliosis) present unsurmountable obstacles to cardiac percussion Furthermore in such cases percussion often provides misleading information Notwithstanding the fact that moderate emphysema is not rare in cardiac patients percussion is and will continue to be however a very important and valuable method for every student and physician so long as x ray machines will not fit into the doctor s bag Those who ridicule percussion or deny the possibility of obtaining information from it deprive themselves of a valuable means of learning at the bedside the size and shape of the heart

Technic

As an aid to reliable and informative cardiac percussion one should mark the borders of the heart as obtained by percussion with a skin pencil (dermatograph) and try to locate the right and left borders This *orthopercussion* provides information about the size and shape of the heart and furnishes results that can be compared in accuracy to those of a postero anterior x ray film

It is well to percuss first the attachment of the right diaphragm or the lower border of the right pleural sinus for percussion of the dome of the diaphragm is unreliable In about 67 per cent of normal adults small dilated cutaneous veins (pleural sinus veins) indicate the site of the pleural sinuses The presence of these veins does not indicate pulmonary cardiac pleural or hepatic pathology as is often suggested Rather the veins are physiologic structures most obvious in those engaged in athletics or heavy physical work (Burrett and Scherf) and are more pronounced in patients with an obstruction of the superior vena cava Figure 1

shows very pronounced pleural sinus veins in a patient with a mediastinal tumor (lymphosarcoma) Smaller chains of veins are seen in normals



FIG 14 Pleural sinus veins in a patient with a mediastinal tumor

After determining the border between the lowest part of the lung and liver which can be obtained with very light percussion the right border of the heart is mapped out Percussion is performed in the interspaces from right to left In mapping out the left cardiac border one starts at the second interspace When the

lower half of the left cardiac border is reached the examiner attempts to keep the plessimeter finger parallel to it and disregards the interspaces

One question arises very often Should the first suggestion of diminished resonance or a very distinct dullness be considered as the cardiac border? If the former is used and the heart is enlarged impairment will be found at some distance from the heart On the other hand very light percussion obtains the area of absolute dullness this shows only how much of the heart is uncovered by lung and yields little information about cardiac size and shape For the best results the beginner should mark the border at points where the difference between two successive percussion strokes is most distinct

The examiner should never draw a line upon the discovery of a dull area but instead should mark it with a dot In this way the subjective aspect of percussion is reduced

Experience gained in the instruction of many groups of undergraduate students *in physical diagnosis has shown the inadvisability of giving general or specific rules concerning the force used in percussing different parts of the right* or left borders Such rules confuse rather than help the beginner Practice alone provides the necessary experience and makes it possible to consider such numerous variables as the shape of the thorax the amount of subcutaneous fat the resonance of the thoracic cage etc

To avoid errors created by diaphragmatic elevation and to obtain sharper dullness percussion should be performed whenever possible with the patient standing In this position the heart approaches the anterior chest wall so that the changes on percussion are clearer and more distinct When percussion is performed on a bedridden patient right handed individuals should always stand on the left side since otherwise the plessimeter finger could not be kept parallel to the cardiac border

Patients with a high diaphragm as well as those with right ventricular dilatation often have a definite dullness at the lower sternum

Much more important than the determination of the *transverse diameter of* the heart either by percussion or x ray examination is the establishment of the cardiac shape Thus in enlargement of the outflow tract of the right ventricle the heart assumes a mitral shape i e filling of the waist line This derives from *the almost perpendicular position of the outflow* tract of the right ventricle The transverse diameter of the heart may be normal In enlargement of the outflow tract of the left ventricle displacement of the apex beat downward and outward is of diagnostic value here as well the transverse diameter of the heart may be normal

Right Cardiac Border

The lower half of the right border is formed by the right *atrium (figure 10a)* Rarely the right ventricle contributes a very short section to the lowest *portion* of the right cardiac border just above the diaphragm Here the inferior vena cava and the hepatic veins may become visible on x ray with a low position of the

diaphragm The upper half of the right cardiac border is formed by the superior vena cava and the innominate vein but these structures do not play an important role in percussion In many normal subjects particularly in elderly people the ascending aorta participates in the formation of the right cardiac border

On x ray examination the atrial portion of the right border i e approximately the lower half extends about twice as far beyond the vertebral column as the upper half of the cardiac border The dullness produced by percussion of the right lower border under normal conditions projects no more than 5 mm beyond the right edge of the sternum this value may be greater in patients with a high diaphragm

Any dullness beyond this limit in the region of the right lower cardiac border often means enlargement of the right atrium especially when the dullness is clear and superficial Roentgenologically dilatation of the left atrium may cause the right border to protrude farther Enlargement of the right or the left ventricle may also displace the right atrium to the right In hydrothorax percussion of the border of the right atrium is performed most satisfactorily with the patient in the recumbent position for the effusion if not too extensive moves posteriorly in such cases percussion sometimes yields better results than roentgenography

Dullness to the right of the upper half of the right sternal border for all practical purposes and insofar as cardiovascular alterations are concerned always stems from an abnormality of the ascending aorta Normally the aorta is not sufficiently wide or sufficiently superficial to provoke any dullness at this area Dilatation and elongation of the aorta forces the vessel to approach the upper sternum and increases dullness over the manubrium sterni

Left Cardiac Border

The left border of the heart may be divided into four parts formed from above downward by the aortic knob the pulmonary artery the left atrium and the left ventricle (figure 10a) The aortic knob which is formed by the sagittal portion of the transverse aorta is absent in infants and children since they do not have any sagittal section (the aorta proceeds diagonally from the right anterior part of the chest to the left posterior aspects) Percussion of this area is not informative because of the deep position of the aorta

Normally percussion reveals no dullness over the pulmonary artery and the left atrium Only a very small section of the left atrium the tip of its appendix participates in the formation of the left cardiac border The mass of the left atrium is located dorsad Under normal conditions one can percuss in the second and third left intercostal spaces from the axilla to the sternal border without encountering dullness This segment of the left border is called the waistline of the heart

Under physiologic conditions a small portion of the left cardiac border above the appendix of the left atrium is formed by the pulmonary artery The remaining and major part of the left cardiac border swinging in a long arc to the cardiac

apex is formed by the outflow tract of the left ventricle which also represents the apex Most of the left ventricle is situated dorsad The right ventricle lies just under the chest wall anteriorly and does not contribute to the formation of the normal left cardiac border

Dilatation of the descending aorta cannot be discovered by percussion of the anterior chest wall Occasionally dorsal percussion to the left of the spinal column elicits some dullness if the descending aorta is dilated

Mitral Configuration

Enlargement of the conus area (outflow tract) of the right ventricle as well as dilatation of the pulmonary artery and the left atrium provoke an easily detected dullness at the second and third left intercostal spaces near the sternum Thus the waistline of the heart straightens and one speaks of mitral configuration of the heart Since the discovery of parasternal dullness in the second left intercostal space readily permits the diagnosis of increased tension in the lesser circulation it has great clinical significance

The term mitral configuration is only descriptive and indicates more or less complete disappearance of the waistline it does *not prove the existence of a mitral lesion* Mitralization *is absent in early stages of mitral disease on the other hand it may be pronounced without presence of mitral disease e g in hypertensive heart disease or in aortic valvular lesions when there is back pressure and hypertension in the lesser circuit Sometimes under these circumstances a relative mitral insufficiency may al o contribute to the development of mitralization* Mitralization *is common in cor pulmonale*

The individual components of the left heart border cannot be distinguished in infants and children for their hearts normally show mitral configuration with a relatively straight left cardiac border The heart is globular in form If an adult has a high diaphragm which shoves the heart upward in the midline the waistline may disappear creating mitralization Since this often happens in women the term female heart has gained some currency Mitralization is also found when the low diaphragm fails to support the heart from below causing the left border to straighten (figure 6c) Mitralization is also seen sometimes when the right diaphragm is unusually high and it is common in kyphoscoliosis In all these instances fluoroscopic study of the heart in oblique positions usually permits the examiner to decide whether an enlargement of the outflow tract of the right ventricle or dilatation of the left atrium causes the mitralization

Aortic Configuration

If the left ventricle alone is enlarged the cardiac waistline becomes accentuated resulting in a condition called aortic configuration of the heart Usually this change of shape can easily be detected by percussion Aortic configuration signifies nothing more than a sharper angle on the left heart border with a large left ventricle it does not mean aortic disease Since it is present whenever the

left ventricle dilates it is a common finding in certain stages of hypertensive cardiovascular disease in diseases of the aortic valves and in myocardial lesions If a patient has a high diaphragm the apical area of the heart may be displaced upward and to the left to cause an aortic configuration this is often wrongly attributed to an enlarged left ventricle (figure 6a)

Fat Pad

In fluoroscopy and in chest films the lower left border of the heart often seems elongated so that its lowest part exhibits a concavity or (sometimes in inspiration) a convexity outwardly directed This is caused by an accumulation of fat (Fett buerzel) between the layers of the parietal pericardium and the mediastinal pleura (Schwarz) The presence of this fat pad is not restricted to obese people It is usually less dense than the heart is at the apical area Occasionally a fat pad found at the lower right cardiac border is confused with a tumor or a diverticulum

Concluding Remarks

Despite the limitations that emphysema or chest deformities impose upon percussion the method is very useful for discovering dilatation of the heart to the right Moreover percussion is valuable for detecting mitralization especially when the latter *stems from enlargement of the outflow tract of the right ventricle* This tract is located ventrad and produces marked dullness in the second left intercostal space parasternally The aortic configuration in the lesions enumerated above is easily percussed

It will be shown in the chapter on pericardial diseases that percussion is also of major importance in the discovery of a pericardial effusion

Details of percussion and of changes in cardiac shape will be discussed in connection with the individual cardiac lesions

AUSCULTATION

At birth the heart rate is about 180 beats per minute but falls considerably in the following hours

It may be said *that normal cardiac action leads to the appearance of four* sounds all of which are occasionally audible They will not be described here in the order of their appearance to avoid confusion we shall begin with the classical first heart sound

(1) The *first* heart sound is composed for the most part of vibrations caused by closure of the mitral and tricuspid valves To what extent vibrations caused by the contraction of ventricular muscle are a factor is still a matter of contro versy (Dock) The opening of the semilunar valves the vibrations caused by atrial systole and the distension of the ascending aorta and proximal part of the pulmonary artery at the beginning of systole may contribute but certainly only to a small degree The first heart sound appears approximately 0 02 second after the beginning of the QRS complex in the electrocardiogram and lasts between 0 14 and 0 16 second in the phonocardiogram Its loudness — as we shall see —

depends upon the position of the atrioventricular valves at the beginning of systole and upon the anatomic condition of these valves it is louder in anemia

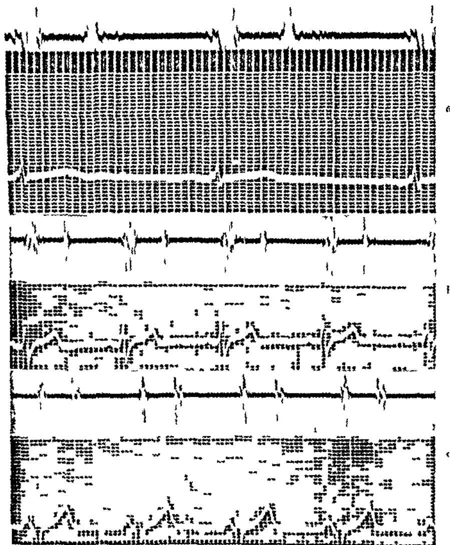


FIG 15 (a) The phonocardiogram and electrocardiogram (lead II) obtained over the cardiac apex from a 22 year old without evidence of cardiovascular disease the vibrations of the loud first heart sound are preceded by coarse vibrations caused by atrial systole there is a faint systolic apical murmur slow and low vibrations of the third heart sound follow those caused by the second sound Figure 15b and c were obtained from a 15 year old male with the microphone over the apical area and over the second left intercostal space parasternally In (b) the first heart sound reveals two groups of vibrations in (c) the second pulmonic sound is split

cardiac neurosis hyperthyroidism fever and mitral stenosis In the phonocardiogram two chief groups of vibrations can be discerned (figure 15a)

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impact murmur which occurs when a jet of blood strikes a part of a vessel a false tendon or a section of a cardiac chamber at a certain distance (Bondi)

False tendons and some aortic insufficiencies cause cooing murmurs like the cooing of a dove or the cry of a seagull These murmurs show regular vibrations in the phonocardiogram

The murmurs heard in healthy subjects will be discussed in detail in the section on mitral insufficiency It may be noted by way of anticipation that they are always systolic are most common in young people but also appear in adults particularly when the velocity of blood flow is increased They are said to be different in loudness and to disappear with a change of posture this however is not unusual in murmurs caused by organic heart disease They are also said to change their loudness with deep inspiration or expiration Such change is rare with murmurs caused by organic heart disease but since it also takes place in normal persons it cannot be used for a differential diagnosis

The system of grading murmurs introduced by Levine is useful A grade 1 murmur is one which is just audible while a grade 6 murmur is so intense that it can be heard without a stethoscope at a distance from the chest wall Grade 5 murmurs are the loudest heard with the stethoscope on the chest but are not audible at a distance Grade 2 murmurs are soft but easily heard From this it will be easy to judge grade 3 (loud murmur) and grade 4 murmur (very loud) so that in actual practice different observers grade murmurs accurately Murmurs from grade 3 to 6 are said never to be found in healthy subjects We would like to modify this statement to the effect that organic disease is *usually* present when such murmurs are heard On the other hand it must be stressed that grade 1 and 2 murmurs may be encountered in people with organic heart disease such as mitral regurgitation

Some murmurs e g of mitral stenosis an interventricular septal defect and a patent ductus arteriosus are almost characteristic They are rarely found in other lesions and then other signs permit the differentiation

Murmurs are not always heard best over the auscultation area of the valve from which they originate Diastolic murmurs of aortic regurgitation are often heard over the lower left sternal border A systolic murmur caused by aortic stenosis may be detected only over the apex if emphysema prevents its appearance in the second right intercostal space These and other related findings will be discussed in detail in appropriate sections

Phonocardiography

With respect to the murmurs that appear in the heart the human ear is an imperfect instrument Vibrations of 20 or less per second are not audible but such vibrations and even those as low as 15 per second occur in mitral stenosis High pitched sounds may occasionally obscure low pitched ones Phonocardiography which is almost as old as electrocardiography can often assist in detecting

abnormal vibrations moreover it keeps a documentary objective record of the auscultatory findings Although a less subjective method than auscultation it rarely contributes to the diagnosis based on the existence of murmurs It does aid however in the analysis and differentiation of split sounds gallop rhythms and abnormal clicks

The phonocardiogram may be obtained with three different types of micro phones (1) the linear microphone which magnifies all vibrations uniformly and reproduces particularly well the very low frequency vibrations which nor mally are not heard (2) the stethoscopic microphone which does not reproduce the low vibrations due to the apex beat and the like (these have no value in clinical auscultation) but which magnifies the others to the degree they would be heard were our ear a more perfect instrument and (3) the logarhythmic micro phone which attenuates low frequency vibrations but increases those heard by the human ear on a logarhythmic scale Because of the excessive amplification the linear microphone method is not practical The stethoscopic microphone yields more than just auscultation alone and is best used in clinical studies while the logarhythmic microphone records high pitched vibrations well and is most practical in the verification of clinical impressions

Practical Advice

Auscultation should be performed with the patient in the upright and in the recumbent position Some murmurs such as the diastolic murmurs of aortic valve insufficiency are more audible when the patient stands while mitral mur murs especially those of mitral stenosis are heard better or exclusively when the patient is recumbent Sometimes the latter murmurs are detected only when the patient is lying on his left side Whenever possible the heart should also be auscultated after exertion Some murmurs like the low pitched ones of mitral stenosis are confused with split heart sounds Such a mistake is understandable since from the standpoint of the physicist the physiologic heart sounds are in reality murmurs The French are more nearly correct when they speak of the first and second bruit of the normal heart

For high pitched murmurs a stethoscope possessing a diaphragm chest piece should be used the diaphragm filters low pitched vibrations while the bell receiver facilitates the discovery of low pitched murmurs The ear pieces of the stethoscope should fit well into the auditory canal of the examiner and both should run in the same direction

The most difficult task for beginners is the differentiation of the heart sounds With a normal rate or bradycardia it is easy to determine which sound is the first and which the second but with a tachycardia this task becomes more diffi cult unless the apex beat or carotid pulse is palpated simultaneously Therefore beginners should never listen to the heart without simultaneously palpating the carotid pulse All auscultatory phenomena synchronous with the carotid pulse are systolic Palpatory or auscultatory signs before or after this are diastolic

Many mistakes would be avoided if auscultation were regularly done with one finger resting on the carotid artery

Since details about auscultation are presented in other chapters only a few general facts will be mentioned at this time

Modification of Sounds

The first heart sound is accentuated more often as the result of hyperexcitability of the heart than of organic cardiac disease Frequently very distant and faint sounds suggest pulmonary emphysema rather than myocardial weakness With a few noteworthy exceptions which are discussed elsewhere no conclusions should be drawn concerning the state of the myocardium from the loudness of the heart sounds Subsequently it will be shown that the first or second sound may become *accentuated or disappear in a host of conditions even in the absence of* intrinsic cardiac damage

Impurity or splitting of the first or second heart sounds are common findings in healthy individuals and particularly in young people On the other hand they are frequently due to cardiac abnormalities The difference in time between the two parts must be at least 0 06 second in order to be perceptible (Luisada) In rare instances splitting is heard when the interval is only 0 03 second

Splitting of the first heart sound is heard best during expiration and at the apex in a healthy person It is ascribed to asynchronous closure of the mitral and tricuspid valves This splitting is not rare in the hyperexcitable heart of cardiac neurosis hyperthyroidism the hypertrophic heart of kyphoscoliosis or fibrotic pulmonary tuberculosis It may be caused by the vibrations of atrial contraction It causes confusion with the murmur of a mitral stenosis Splitting of the first sound may be confused with a presystolic gallop rhythm and a systolic click in pulmonary hypertension or in pericardial adhesions

Systolic clicks will be discussed in the section on gallop rhythm

Duplication of the second heart sound heard best in the second left intercostal space is believed to result from a short difference in time between the closure of the aortic and pulmonic valves (figure 15e) The first part originates in the aortic the second in the pulmonary valves Paradoxical splitting of the second *heart sound in which the aortic component appears after the pulmonary one is* seen in left bundle branch block and in aortic stenosis It is explained by prolongation of the duration of systole of the left ventricle (Gray)

The phenomenon is heard best and often exclusively over the pulmonary artery in the second left intercostal space and the question arises whether asynchronous closure of the pulmonary valves alone is responsible With the artificial ball valve of Hufnagel for surgical treatment of aortic regurgitation splitting of the second sound may be found (McKusick et al) and may appear when the ball strikes one corner of the orifice before the other This splitting occurs particularly at the end of inspiration and the onset of expiration It is absent in complete pulmonary stenosis and is especially pronounced in right bundle branch block (figure 16)

In a large percentage of children and healthy adults during rest (but sometimes only on exertion) the third heart sound is heard physiologically over the lower end of the sternum and at the apex In some individuals this low pitched sound is very loud but in others it is scarcely audible It may appear and disappear with the different phases of respiration About 95 per cent of healthy children have a physiologic third heart sound (Steinberg) and it has been observed in 42 per cent of medical students Thayer found a third heart sound in 65 per cent of his normal subjects We occasionally found it during routine examinations in

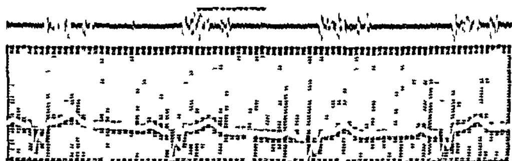


FIG 16 Right bundle branch block (lead II) The phonocardiogram was recorded with the microphone in the second left intercostal space It shows splitting of the second sound

individuals up to but not beyond 25 years of age Some claim to have heard it in normal people as old as 40 It is easily confused with gallop rhythm This triple heart rhythm is best heard in and median to the apical area It may be missed in the erect posture

Some investigators explain that the third heart sound derives from a stretching of the myocardium during the diastolic inflow of blood while others believe that normal filling causes a sound produced by the impact of the ventricles on surrounding tissues But this theory does not explain the fact that the third heart sound can also be heard in the exposed heart It is more probable that the stretching of the fibrous tissue in the chordae tendineae or vibrations of the valves (Lewis and Dock) causes the third heart sound at the beginning of diastole Increasing thickness of the chest wall or in the opinion of others the gradual reduction of cardiac elasticity with increasing age makes the third heart sound disappear

On the small normal chest of children without heart disease but with cardiac hypermotility and more often in children and adults with enlarged hearts a soft grating systolic friction rub is heard The rub may be noted in systole as well as in diastole and it may disappear on deep inspiration This phenomenon results from friction created when the normal epicardium rubs against the normal parietal pericardium It is most frequently detected in hypertensive patients with large left ventricles when they are in the left lateral recumbent position Usually this friction sound is transient It is often noted in connection with the hyperexcitable heart of hyperthyroidism (Goodall) and in this instance it may be

limited to the area over the conus of the pulmonary artery i e the most prominent part of the heart The evaluation of all the clinical data usually permits the differentiation from the friction rub caused by pericarditis

Pulmocardiac murmurs or respiratory heart murmurs are heard most commonly along the left cardiac border They are explained by pulmonary compression when the heart enlarges in diastole or by pulmonary expansion when the heart becomes smaller in systole since air may be thus expelled or drawn into a section of lung thereby producing rales or a murmur Ordinarily a little experience will permit differentiation from an endocardial murmur Naturally these phenomena are more frequent when the heart is enlarged They are heard best over the lingula of the lung near the conus of the pulmonary artery In this area rales are often audible in one or the other phases of the cardiac cycle (cardiopulmonic rales)

More often in children but occasionally in adults particularly with anemia a venous hum may be heard over the base of the heart transmitted from the large veins of the supraclavicular area The hum is continuous and shows a diastolic accentuation since blood flows faster in the veins in ventricular diastole This murmur is mentioned in the chapter on aortic insufficiency and anemia

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Chapter 5

Compensation and Decompensation

Cardiac Reserve and Compensation

A fundamental property of heart muscle is an ability to accommodate its activity to the requirements of the organism This adaptibility is what makes life possible since it permits the heart to increase its stroke and minute volumes and thus meet greater demands of the body during exertion digestion pregnancy and innumerable other situations The amount of blood expelled by the heart may increase from 5 to 7 liters per minute at rest to 25 or 30 liters during vigorous exercise The myocardium does not utilize all its potentialities during rest a reserve force is available and is brought into play whenever the filling of the heart increases Within certain limits Starling s law can be applied to the healthy heart i e greater stretching of the myocardial fibers by increased cardiac filling causes a stronger contraction

During exertion large amounts of blood are returned rapidly from the muscles and blood depots to the right heart so that its contents increase The left heart thus receives and expels more blood and the output per minute rises In some patients an increase of blood pressure offers added resistance to the discharge from the left ventricle which does not empty completely for a few beats This increases the amount of residual intraventricular blood at the end of systole slightly distends the left ventricle and stretches the cardiac muscle fibers thus systole becomes stronger even when the inflow from the atrium remains constant After a few beats cardiac output is the same as before the elevation of blood pressure

Under physiologic conditions the output of the heart per minute can be increased in another simple manner namely by acceleration of cardiac rate If the tachycardia does not exceed certain limits (about 120 beats per minute) the diastolic filling is not impaired and therefore the output per minute of the heart will be markedly increased

Under pathologic conditions the heart endeavors to adapt itself as we shall see to the changed situation by means of similar mechanisms i e it attempts to compensate for the consequences of the disease If the heart succeeds in supplying an adequate amount of blood to every part of the body so that sufficient quantities of oxygen reach all tissues while metabolites like carbon dioxide are speedily removed and congestion is avoided one speaks of a compensated circulation The chief goal of compensation is to deliver a normal minute volume not

only at rest but also when demands are moderately increased If the cardiac reserve is decidedly diminished with the result that the circulation is adequate only at rest or with very restricted effort such as walking on level ground while ascent of stairs causes distress the condition borders on decompensation If the faltering heart can no longer accomplish its tasks and symptoms perhaps trifling at first gradually or suddenly become worse one speaks of failing or broken compensation or decompensation The term congestive heart failure is also employed when the circulation is no longer adequate and passive congestion (increased venous pressure in the lesser or systemic circulation) is present even during rest To be sure the concept of decompensation is rather hazy which accounts for the bewildering variety of definitions that have been advanced

BACKWARD AND FORWARD FAILURE

The mechanism of cardiac failure has interested physicians for more than a century The theory that the cavity behind the failing one suffers first — an idea propounded by Hope as early as 1842 — was widely accepted and subsequently supported by Starling s experiments Blood dams up behind the failing ventricle Thus with insufficient systolic emptying of the right ventricle the amount of residual blood at the end of systole is increased the diastolic pressure in the right ventricle is higher and the normal inflow of blood from the right atrium is impeded the pressure in the right atrium rises until an effective pressure gradient is re established causing increased venous pressure With failure of the left ventricle similar changes occur in the left atrium and the lesser circuit All this leads to a diminished cardiac output In order to maintain a normal blood pressure a reflex arteriolar constriction occurs This causes peripheral hypoxia and stimulates the bone marrow Blood volume increases (Starling)

This back pressure theory is still valid Early voices were raised however pointing out that some phenomena particularly paroxysmal dyspnea in cardiac patients are better explained by the diminished output of the failing heart (forward failure theory) With the introduction of cardiac catheterization and the possibility of determining cardiac output with greater accuracy the occurrence of a diminished output in patients with a failing left ventricle as the result of hypertension coronary sclerosis or aortic valvular lesions was confirmed These investigations and the determination of the renal blood flow (see below) induced many physicians to explain all signs of heart failure by forward failure According to this conception ventricular failure and the ensuing diminution of cardiac output lead to a reduced blood supply to the kidney causing diminished excretion of sodium and water The increase in blood volume is the reason for the elevated venous pressure For many practitioners the old concept of backward failure was a thing of the past and the new theory was believed to be the only one to explain all signs of heart failure

Critical evaluation of the data obtained in the laboratory and clinical observations in particular show that the rejection of the back pressure mechanism

is unjustified We often see within a few hours the development of an enlarged liver and congestion of the peripheral veins in patients with atrial fibrillation or paroxysmal tachycardia with a rapid ventricular rate Rentention of water and increased blood volume could not play a part so soon Daily clinical experience reveals a marked pulmonary congestion but no increase of venous pressure or peripheral edema in patients with left ventricular failure or in patients with mitral stenosis and diminished cardiac output The pulmonary congestion in mitral stenosis diminishes when right ventricular failure supervenes On the other hand patients with pericardial adhesions or cor pulmonale with failure develop peripheral venous congestion and enlargement of the liver without any other signs of cardiac failure

Thus the back pressure mechanism does play a great part in the development of signs and symptoms of cardiac failure It is possible that it is the dominant mechanism in acute failure with the consequences of forward failure determining the picture in chronic heart failure (Dock)

The emphasis that has been laid upon the forward failure mechanism in recent years has aided in a better understanding of some aspects of heart failure Thus the influence of peripheral vasoconstriction — considered by Starling long ago — was completely neglected and only now has become better appreciated In a similar manner the increased amount of circulating blood in cardiac failure has been known for many years but its importance for the explanation of some features of cardiac failure is at present better understood

Cardiac catheterization enabled us to distinguish another type of cardiac failure high output failure It was found by investigators using methods available before cardiac catheterization for the determination of cardiac output that occasionally the cardiac output per minute was high despite the presence of failure In patients with emphysema and a lower oxygen saturation of the arterial blood hyperthyroidism with an increased oxygen consumption anemias with a disturbed oxygen transportation arteriovenous fistulas Paget s disease with an increased venous return and finally in beriberi disease with an abnormal tissue metabolism the circulation is markedly accelerated The cardiac output per minute at rest in anemia may amount to 10 liters in emphysema with marked oxygen undersaturation of the arterial blood it has been found to be 6 to 10 liters per minute If congestive failure develops the output falls but it is still higher than it is in patients with primary heart disease

Thus the mechanism in this group of patients does not differ from others When the heart fails the tissues are supplied with less blood than they need

MECHANISMS OF COMPENSATION

Compensation by Cardiac Dilatation

The importance of dilatation of the cardiac chambers for compensation becomes clear if we recall the changes following experimental valvular lesions An immediate result of aortic regurgitation is an increased flow of blood into tl

left ventricle This structure receives a normal amount of blood from the left atrium plus the blood regurgitating from the aorta The increased content causes a stronger contraction and the output is larger by the volume of regurgitated or pendulum blood Despite the loss of some aortic blood by regurgitation during each diastole the minute volume remains normal If a marked aortic stenosis is created experimentally increased resistance prevents complete emptying for a few beats until the diastolic volume of the heart and the diastolic tension of its muscle fibers increase sufficiently to permit the output to reach a normal value The mechanism of compensation in hypertension operates in a similar way In myocardial lesions incomplete emptying of the heart is a factor in the dilatation

Hence dilatation of the cardiac chambers may be produced by any of these mechanisms i e increase of cardiac contents by regurgitation by augmented resistance to outflow (insufficient emptying) and finally by greater venous return The extent of cardiac dilatation is limited by the pericardium Dilatation permits the heart to maintain its output and within broad limits to compensate for abnormalities within the circulatory apparatus This dilatation is often minimal and cannot be recognized clinically or even by x ray examination

If the heart is unable to compensate for the lesion by means of the initial slight increase of filling and hypertrophy discussed above the amount of residual blood will increase and the dilatation is greater Thus a dilated heart is not necessarily a failing heart on the contrary dilatation is often a compensatory measure The left ventricle may dilate tremendously in aortic regurgitation and all signs and symptoms of heart failure may be missing However when the dilatation surpasses a certain limit cardiac output decreases

In normals it has been calculated that the residual blood within the cardiac chambers may amount to 50 ml rising as high as 2000 ml in cardiac failure

Compensation by an Increase of Rate

Another mechanism for rapidly increasing the output is a moderate acceleration of the heart rate While this may decrease diastolic filling of the heart somewhat the increased number of beats per minute may offset this and the net result may be a larger or even doubled minute output In many heart lesions acceleration that derives mainly from reflex action occurs very early

An increase of intraventricular pressure causes an immediate rise of pressure within the corresponding atrium for it is mainly the difference in pressure between the atrium and ventricle which causes ventricular filling Elevation of intra atrial pressure and the consequent dilatation of its wall and the walls of veins leading to the atrium cause a reflex tachycardia by means of the Bainbridge reflex The path of this reflex utilizes vagal and in part sympathetic fibers The effect of the reflex is diminished by atropine and disappears after extirpation of the stellate ganglion The exact location of the receptors is uncertain It is possible that no reflex is needed because when the right atrium is dilated the stretch

exerted on specialized fibers of the sinus node suffices to make the latter form faster impulses

Tachycardia appears very early in aortic insufficiency but in this instance a carotid sinus reflex is activated by the low mean blood pressure at the carotid sinus

While an acceleration of rate sinus tachycardia is often a useful measure of maintaining the minute volume in some conditions it may be harmful In mitral stenosis the tachycardia shortens diastole further hampering the filling of the left ventricle and adding to the pulmonary congestion As will be shown later a tachycardia increases oxygen requirements of the heart muscle and if the demand cannot be satisfied owing to disease of the coronary arteries myocardial nutrition suffers and the frequency of anginal attacks increases

Compensation by Hypertrophy

In cardiac hypertrophy the size of the myocardial fibers increases This increase in size always follows a primary dilatation since the fibers do not enlarge unless they increase in length and gain in tension Cardiac hypertrophy was fully developed in dogs within 80 days after an experimental lesion The border line is not sharp between physiologic cardiac hypertrophy of healthy athletes or people engaged in heavy physical work on the one hand and the hypertrophy consequent to increased filling or greater resistance on the other Hypertrophy enables the heart to perform the added task made necessary by greater filling However it also necessitates a much greater blood supply although there is no evidence to show that the number of capillaries increases in the hypertrophied heart Hence the size of the muscle fiber that can be adequately nourished by one capillary is limited There are reasons for believing that in some conditions e g stenosis of the aortic valve the hypertrophy reaches a point at which some layers of heart muscle are inadequately nourished and hypoxia of the myocardium results Furthermore the nuclei of the heart muscle cells do not grow and their number does not increase in hypertrophy Therefore limits are established for the growth of the protoplasm in hypertrophy

Whereas tachycardia and cardiac dilatation occur immediately if the need arises hypertrophy develops slowly when the added load for the heart has existed for some time Although hypertrophy does not appear without antecedent dilatation the latter may be too slight for demonstration by clinical methods This type of hypertrophy is called *concentric hypertrophy* a rather common occurrence in the left ventricle of patients with hypertension or in those with an aortic valve stenosis it is found in the right ventricle if a disease elevates the blood pressure in the lesser circuit When hypertrophy and more marked dilatation coexist the term *excentric hypertrophy* is used This form is encountered in the left ventricle in aortic regurgitation in connection with myocardial lesions or in coronary sclerosis If concentric hypertrophy changes to excentric hypertrophy one may assume that cardiac reserve is diminishing The evolution of this process may however require a considerable period of time

Raab stresses hormonal factors in the genesis of cardiac hypertrophy He refers to the large heart seen in acromegaly and the absence of hypertrophy after ligation of the aorta when an hypophysectomy had been done before

CHANGES IN THE AMOUNT OF CIRCULATING BLOOD AND OF TOTAL BLOOD VOLUME

The volume of circulating blood is reduced in a large number of cardiac patients By retaining a great quantity of blood the engorged liver and the markedly enlarged left atrium tend to prevent pulmonary congestion due to a stenotic mitral valve Accordingly patients with mitral valve disease and a large liver or with an enormous left atrium (aneurysm of the left auricle) often are remarkably free from pulmonary congestion and dyspnea This is understandable if one realizes that more than 2 000 ml of blood may be retained occasionally in the huge left atrium of mitral stenosis

If cardiac weakness or congestion lasts for a long time however the arterial oxygen deficit acts as a constant stimulus to the hemopoietic apparatus This stimulus is responsible for the increased production of red blood cells and an increase of the circulating and total blood volumes Many pathologists have directed attention to the large amount of blood found at necropsy in patients dying of congestive heart failure Such increased volume of circulating blood imposes a great burden on the heart and causes further slowing of the peripheral circulation As the peripheral blood depots become engorged the heart finds it increasingly difficult to adapt itself to the varying requirements

Wollheim distinguishes between minus decompensation (with diminished blood volume) as in myocardial infarction and plus decompensation (with increased blood volume and elevated venous pressure) in the usual type of cardiac failure

INCREASED UTILIZATION OF BLOOD

When contact between the blood and tissues is prolonged oxygen is utilized more completely and consequently the arteriovenous oxygen difference increases this may be a compensatory measure in congestive heart failure Actually the arteriovenous oxygen difference may double in heart failure and it may approximate the situation occurring in exertion In patients with congestive heart failure cardiac output cannot increase on exertion but there is an increase of the arteriovenous oxygen difference

RIGHT AND LEFT VENTRICULAR FAILURE

Mechanism

It is proper to distinguish between failure of the right and the left ventricle although some objections have been raised to the justification of this practice For example it has been stated that weakness of the left ventricle results in a decrease of its output therefore the return of blood to the right heart suffers since this is effected mainly by vis a tergo Accordingly the amount of blood

expelled by the right ventricle decreases to the same extent that the left ventricular output diminishes In this way stasis in the lesser circuit is avoided

Similarly in right ventricular failure less blood is propelled to the left heart so that its output is again reduced in proportion to the fall of right ventricular output Under these circumstances the return of blood to the right heart diminishes and stasis in the great veins and liver does not necessarily appear

While these presumptions are correct they are applicable only when it is assumed that the volume of circulating blood remains constant and the right heart invariably receives just as much blood as the left ventricle ejects It is this assumption which is incorrect The inflow of blood into the right heart undergoes continual variations for nervous as well as humoral regulatory mechanisms constantly control and adapt the amount of venous return to the heart in accordance with the momentary requirements of the organism A large amount of blood may be stored in depots (liver subcutaneous venous plexus splanchnic veins) if it is not needed and this depot blood may be suddenly mobilized and sent to the right heart if necessary When the inflow of blood increases suddenly the demands upon the heart are greater If the right or left ventricle has no reserve force available it is unequal to the burden causing backward stasis and congestion to develop The early consequence of heart failure is congestion upstream in the veins

In this way pulmonary congestion develops in left ventricular failure while hepatic congestion and engorgement of the systemic veins follow failure of the right ventricle If the entire heart is equally and simultaneously damaged so that both ventricles fail at the same time the clinical picture is the same as in ordinary right ventricular failure because congestion develops upstream of the heart with the result that hepatic enlargement and venous engorgement occur in the absence of pulmonary congestion This happens in cases of diffuse myocardial damage as in diphtheria and rheumatic fever Hepatic congestion is also seen in association with paroxysmal tachycardia or atrial fibrillation with a rapid ventricular rate With a tachycardia both ventricles contract rapidly and the inflow of blood into the right heart is impeded by the brevity of diastole

Relief Afforded by Right Ventricular Failure

In patients with pulmonary congestion and dyspnea the onset of right ventricular failure may afford speedy and remarkable relief If pulmonary congestion has become extreme and dyspnea and orthopnea have attained great intensity right ventricular failure with engorgement of the liver and systemic veins may change the situation completely Dyspnea and orthopnea diminish the vital capacity increases and x ray reveals less pulmonary congestion Naturally the development of peripheral edema and hepatomegaly now create new complaints but the dyspnea which harassed the patient day and night has lessened Since the patient soon becomes more or less accustomed to the discomfort evoked by the hepatic engorgement and since mercurial diuretics satisfactorily control the edema the grateful patient considers the new situation a vast improvement

This unloading of the lesser circuit fails to occur only when the state of the patient is precarious because of advanced pulmonary congestion Often the right heart is involved from the start and therefore pulmonary congestion of a high degree never develops Thus patients with rheumatic mitral stenosis who have a simultaneous tricuspid regurgitation need not within certain limits suffer from dyspnea or orthopnea If however the right heart works normally in a patient with mitral stenosis extreme pulmonary congestion may result since the barrier raised by the stenotic valve prevents blood from entering the left ventricle When it is recalled that a congested liver can retain approximately 1 500 ml of blood the relief of pulmonary congestion afforded by hepatic engorgement becomes comprehensible

Bernheim s Syndrome

In pronounced hypertrophy and dilatation of the left ventricle signs of right heart failure may appear without a preliminary period of pulmonary congestion Clinical observations by Bernheim suggested that in such cases the interventricular septum may bulge into the right ventricle and prevent a normal inflow of blood from the systemic veins The Bernheim syndrome is said to be especially encountered in patients with aortic stenosis and hypertension with marked cardiac hypertrophy A similar phenomenon has been seriously considered by physiologists On the basis of personal clinical and postmortem observations we accept the *possibility* of this mechanism although proof of its occurrence in patients with left ventricular hypertrophy is lacking The role this mechanism could play in diminishing back pressure in the lung and in relieving dyspnea is obvious

The only instances in which we consider this syndrome proved are cases of septal infarction with an aneurysmal bulge into the cavity of the right ventricle

Concluding Remarks

These observations show again how a multitude of factors interact in the production of different cardiac symptoms so that it is not advisable to infer the degree of heart failure from the severity of pulmonary symptoms

It should be clear that in practice right and left ventricular failure do not always appear in pure form nor do they have to appear in sequence for the clinical syndromes just discussed to emerge clearly Not rarely there is evidence of pulmonary as well as moderate congestion in the systemic circulation so that signs of right and left ventricular failure coexist Nevertheless an awareness of the rules outlined in this section may facilitate an understanding of both the variations in patients complaints and objective findings in the different stages of decompensation

DIAGNOSIS OF HEART FAILURE AND CONGESTION

To recognize the beginning of heart failure is difficult and often impossible Pulmonary congestion may be detected by careful interrogation designed to

elicit the subjective symptoms that accompany the condition Heart failure may be recognized by physical examination and by the evidence provided by roentgenography measurement of circulation time and venous pressure

One of the fundamental rules in the diagnosis of every case of heart failure is to endeavor to ascertain the reason for its occurrence Myocardial failure may be caused by excessive strain or by a primary disturbance of the myocardial fiber It is rare for the heart to fail gradually because of progressive dilatation Very often failure is precipitated by pulmonary embolism or paroxysmal atrial fibrillation in other instances an acute infection such as streptococcal tonsillitis or pharyngitis is responsible Among 300 patients with heart failure a respiratory tract infection was found in 167 in 150 it was the cause of heart failure (Flint) Overeating increase of weight mental and physical strain and progressive coronary sclerosis may be precipitating factors

If the precipitating cause is known its eradication can lead to a decided improvement of long duration This happens if atrial fibrillation with rapid ventricular rate is successfully treated with digitalis if foci of infection which damage the myocardium are removed if an anemia is abolished or if the patient recovers from a pulmonary embolism

According to Hegglin myocardial failure may be of hemodynamic origin that is it may result from fatigue and overexertion it may also be of energetic dynamic origin resulting from a primary disturbance of the heart muscle itself Energetic dynamic heart failure is a form of heart failure in which a shortening of the mechanical systole and a prolongation of the Q T interval are found (Hegglin) According to the author a heart in an abnormal metabolic state cannot maintain a systole of sufficient duration With a damaged myocardium the hemodynamically efficient systole is shortened (Wiggers) and this diminishes cardiac output If the blood supply to the myocardium via the coronary arteries is inadequate the heart becomes fatigued more quickly

Stimulation of receptors of the Jarisch Bezold reflex in the myocardium leads to an increased vagus tonus the heart is slowed and peripheral vessels dilate to protect the heart from overfilling

Clinical Diagnosis of Pulmonary Congestion

Clinical demonstration of pulmonary congestion may be so difficult that reliance must be placed upon the history of exertional dyspnea It should always be remembered however that dyspnea on effort occurs in other conditions e g obesity neurocirculatory asthenia or pulmonary diseases in the absence of congestive heart failure

As will be shown later cyanosis is not an unequivocal sign of pulmonary congestion and the determination of vital capacity yields little information The latter procedure has diagnostic value in slight pulmonary congestion only when comparative figures are available to indicate the status of the same patient prior to the onset of stasis but such information is rarely at hand Even elevation

of the diaphragm may diminish the vital capacity so that absolute values give little conclusive information Moreover accurate measurements are frequently difficult to obtain particularly in women

It should be emphasized that evidence of pulmonary congestion as well as dyspnea on exertion do not always prove that heart failure has occured In some conditions such as mitral stenosis pulmonary congestion is due to the valvular lesion and is present prior to heart failure

With more advanced stasis a cough develops and a brownish sputum is expectorated This sputum may contain macrophages containing hemosiderin i e heart failure cells or cells with a brownish stain If pulmonary congestion sets in abruptly moist crepitant rales are often audible over the bases of the lungs more commonly on the right side than on the left In chronic congestion the rales are often dry Even in the absence of other signs of heart failure the appearance of these rales in patients with conditions causing strain of the left ventricle such as hypertension myocardial or aortic lesions is an indication for digitalis therapy If digitalis is withheld congestion increases and pulmonary edema may occur without further warning This danger may also be averted by mercurial diuretics

The appearance of rales does not depend exclusively upon the severity of the pulmonary vascular engorgement thus in some patients with mitral lesions and pulmonary congestion of long duration relatively few rales and rhonchi are heard or only somewhat roughened expiration and intensified breath sounds are noted In long standing pulmonary congestion sclerosis of the pulmonary arterioles together with increased fibrosis and induration of the pulmonary tissue reduce the amount of fluid in the lung While large quantities of fluids exude from the lungs during necropsy of a patient who died from left ventricular failure caused by hypertension the lungs of patients with mitral stenosis and advanced pulmonary congestion of year long duration are dry Accordingly the absence of rales does not disprove the presence of pulmonary congestion

On the other hand some patients particularly elderly ones have moist rales over large areas of the lungs but principally in the basal region These rales which persist without modification for years despite intensive therapy are due to otherwise asymptomatic pleural adhesions obstructing the local lymphatic channels and causing transudation into the air passages Thus there is simulation of the auscultatory findings of pulmonary congestion

To distinguish between simple pulmonary congestion and infectious bronchitis is not always easy If the temperature is elevated and the protein content of the sputum increased bronchitis is the probable diagnosis However fever sometimes persisting for days is not uncommon in decompensation and is regarded as a consequence of stasis Formation of toxic substances due to hypoxia slowing of the circulation and therefore local disturbances in the thermal regulatory mechanisms in the periphery and lessened heat dispersal are responsible for a moderate rise of temperature If the temperature surpasses one degree Celsius above normal a complication such as pulmonary infarction probably exists

When emphysema is present in combination with fever and rales the findings are sometimes interpreted to be evidence of a primary pulmonary disorder and the underlying cardiac pathology is overlooked This is a common occurrence in those cases in which *no abnormal auscultatory cardiac findings are present*

In pulmonary congestion the second pulmonic sound becomes accentuated but it will be shown later that this sign has only limited clinical value

With progressive failure of the left ventricle dilatation of the left atrium is an *early development* *Hypertrophy and moderate dilatation of the right ventricle* especially of the outflow tract gradually develop and the heart becomes mitralized on percussion

This discussion should make clear that a roentgenologic examination is often indispensable for the demonstration of pulmonary stasis especially in its initial state

Roentgenologic Diagnosis of Pulmonary Congestion

A history of increasing exertional dyspnea aids considerably in the early diagnosis of pulmonary congestion even when physical diagnostic methods yield little pathognomonic evidence Roentgenoscopy and roentgenography are invaluable for providing reliable objective data

Pulmonary congestion causes engorgement of the blood vessels and therefore creates large hilar shadows with increased pulsation and accentuated pulmonary markings It has been estimated that congested lungs may hold twice as much blood as normal ones without increase of pulmonary arterial pressure Congestion of the perivascular and peribronchial lymph vessels contributes decidedly to the increase of pulmonary markings whereas enlargement of lymph glands accentuates the hilar shadows Later cloudiness of the lung fields increases and these changes may be general or circumscribed This cloudiness and mottling is due to transudation into the alveoli distention of the pulmonary capillaries and particularly to the dilatation of the lymphatics Since the lymphatics are more numerous and larger where the large bronchi and blood vessels bifurcate cloudy areas with ill defined borders often appear Formerly these shadows were confused with those of intrinsic diseases of the pulmonary parenchyma (Zdansky)

The lungs become less transparent and the definition of the heart and vessels less distinct *In rare cases of pulmonary congestion the lungs display innumerable* small shadows scattered diffusely throughout and give the impression that miliary tuberculosis may be present Pulmonary congestion causes hemosiderosis and fine granulation resembling pneumoconiosis miliary tuberculosis or Boeck s sarcoid This impression is also created by small bronchi seen end on and filled with heart failure cells

In chronic congestion increased markings and abnormal shadows in the lungs are also due to progressive pulmonary fibrosis (resulting from hyperplastic connective tissue and from reactive and reparative processes following intrapulmonary hemorrhages) *and to sclerosis of the pulmonary arteries* Since intrapulmonic

transudates form predominantly in the poorly ventilated areas local atelectasis may result

A new x ray sign of pulmonary congestion has been described recently by Kerley Two to 15 horizontal lines up to 2 mm in thickness and 0 5 to 1 cm



FIG 17 Kerley lines in the right lung field of a 32 year old patient with rheumatic mitral stenosis

apart and 5 to 15 mm in length are seen in the costophrenic angle perpendicularly to the lateral chest wall They are most common in mitral stenosis but they also appear in pulmonary congestion of other etiology They are called

septal lines since the precipitation of hemosiderin and edema in the interlobular septa is responsible Short found these lines in 25 of 33 patients with severe mitral stenosis

Figure 17 shows Kerley lines in a patient with mitral stenosis and a large left atrium They must be differentiated from blurred vessels which usually communicate with each other In Figure 17 one of the horizontal lines stops short of the vascular shadow while the other extends beyond it

Pleural adhesions as well as local pulmonary indurations the sequelae of old infarctions and hemorrhages account for the irregular distribution of congested areas

When pulmonary congestion develops rather abruptly the lung fields become less clear and clouding appears but there are no hilar changes so characteristic of chronic passive congestion of the lungs

CYANOSIS

An increased amount of reduced hemoglobin in the arterial (capillary) blood is responsible for cyanosis the bluish color of the skin observed in connection with cardiac lesions Cyanosis appears as soon as reduced hemoglobin amounts to 5 Gm per 100 ml of arterial blood Since 1 Gm of hemoglobin unites with about 1 34 ml of oxygen 6 7 per cent oxygen unsaturation will be present when cyanosis appears (Lundsgaard and van Slyke) the normal figure for oxygen unsaturation is approximately 3 5 per cent While the occurrence of cyanosis depends entirely upon the amount of reduced hemoglobin its depth as well as its early discovery are influenced by the thickness of the skin pigmentation and the number of capillaries Cyanosis appears earliest where the skin is thin i e in the lips fingertips and nail beds

If the patient is severely anemic cyanosis never occurs since 5 Gm of reduced hemoglobin per 100 ml of blood the necessary amount cannot be present On the contrary patients with polycythemia and an otherwise normal circulation may display cyanosis constantly because the percentage of oxygen unsaturation per 100 ml of blood easily reaches the critical level

In cardiac patients cyanosis or an increased amount of reduced hemoglobin in the arterial blood may originate in four different ways

(1) In congenital heart lesions the arterial and venous systems often communicate abnormally (malformations of the septa riding aorta transposition of the aortic and pulmonic orifices) and venous blood is shunted into the arterial system The presence of increased amounts of reduced hemoglobin in the arteries of these patients requires no discussion although it should be noted that at least one third of the venous blood must be short circuited for cyanosis to appear

A large percentage of congenital heart lesions however belong to the so called acyanotic group despite the existence of an abnormal communication between the arterial and venous systems as a result of a left to right shunt Normally pressure in the left atrium left ventricle and aorta is higher than in the

right atrium, right ventricle and pulmonary artery. Therefore arterial blood flows into the venous system without venous blood entering the arterial, so that cyanosis is absent. Not infrequently, however, activities like coughing or crying spells or complications like pulmonary or mitral stenosis elevate the pressure in the right heart sufficiently to force venous blood into the arterial side in amounts adequate for the production of cyanosis. Of course, in children crying spells may cause cyanosis under normal conditions owing to the prevention of inflow of blood into the chest during pressing and straining.

(2) Slow peripheral circulation, the result of dilated peripheral vessels or congestion and increased venous pressure, permits prolonged contact between the blood and tissues, thereby increasing oxygen utilization. In this way the amount of reduced hemoglobin in the capillary blood rises (stagnant anoxemia). The cyanosis found in patients with pericardial adhesions and inflow stasis or some cases of right heart failure belongs in this group.

This form of cyanosis also occurs in the absence of heart disease. Not rarely patients are referred for a cardiac examination because they exhibit a striking cyanosis of the lips or fingers; this creates the suspicion that organic heart disease exists. In actuality, nothing more than a slow peripheral circulation resulting from dilatation of the peripheral vessels is present. The causative factor varies. In many cases there is a constitutional widening of the peripheral vessels in some parts of the body; in others, vascular dilatation appears after prolonged exposure to cold weather or by virtue of some disturbance of unknown etiology (acrocyanosis). This type of cyanosis is easily recognized by the cyanotic parts — lips, fingers, tip of the nose or lobes of the ears — feeling cold to the touch. Owing to the retarded circulation, less warm blood than normal enters these tissues per minute; consequently, this kind of cyanosis is called cold cyanosis and can be distinguished from other varieties by palpation.

(3) Cyanosis conceivably may occur when oxygen utilization in the tissues is increased for other reasons. Thus, an increase of the arteriovenous oxygen difference in cardiac patients is an important cause of cyanosis.

(4) The fourth and most important form of cyanosis in circulatory disorders, of which two subvarieties are distinguished, depends upon abnormal oxygenation of the blood in the lungs.

(a) PULMONARY STASIS. If the pulmonary circulation is slow in the absence of any other disturbance, oxygenation of the blood should be excellent, for the corpuscles have a better opportunity for gas exchange with alveolar air. Widening of the capillary bed, however, prevents some of the red blood cells from coming in contact with the alveolar wall. Furthermore, congestion alters the pulmonary epithelium or capillary endothelium and prevents the normal exchange of oxygen. Carbon dioxide, due to its greater permeability, is not retained. The interaction of all these factors is the reason that the depth of cyanosis does not strictly parallel the degree of congestion. Indeed, decided pulmonary congestion may be unaccompanied by cyanosis.

Like the dyspnea of pulmonary congestion cyanosis may diminish if supervening right heart failure and hepatic enlargement reduce pulmonary congestion Rapid failure of the right heart often diminishes rather than accentuates a previously existing cyanosis Such patients may become quite pale because of the large amount of blood that is retained in the liver Marked cyanosis is not a regular sign of right heart failure If such patients show a deep cyanosis an underlying pulmonary disease or severe venous congestion is usually responsible

In pneumonia and more rarely in pulmonary infarction cyanosis may appear when large amounts of blood are shunted from the pulmonary arteries to the pulmonary veins without undergoing arterialization

(b) PULMONARY SCLEROSIS ESSENTIAL PULMONARY HYPERTENSION Primary sclerosis of the larger arteries in the lesser circuit is extremely common Atherosclerosis of these vessels is no rarer than in the systemic circulation Approximately one half of all individuals beyond the age of fifty years exhibit this lesion and senile pulmonary sclerosis is almost invariable in patients over seventy years of age This variety is asymptomatic

Another primary form of pulmonary sclerosis the Averza or Averza Arrillaga syndrome involves the smaller peripheral arteries Its pathogenesis is not clear Syphilis formerly considered provocative does not play any role Bronchopneumonia has been assumed without justification to be the initial lesion Some form of primary arterial involvement may contribute to the development of this disease Such cases may have been instances of essential pulmonary hypertension in which an unknown mechanism increases pressure in the lesser circuit It may be assumed that we are not dealing with a disease entity and that different conditions causing pulmonary arterial hypertension are responsible

Patients with pulmonary hypertension display a deep blue cyanosis (cardiacos negros) and trivial dyspnea This disparity between the depth of cyanosis and the mildness of the dyspnea is remarkable Headache vertigo somnolence cough hemoptysis and anginal pain are typical symptoms A polycythemia which may reach ten million red blood cells per cubic millimeter is common and contributes to the cyanosis Physical examination discloses evidence of right ventricular hypertrophy *The conus of the pulmonary artery and its branches are prominent* and the second pulmonic sound is accentuated A systolic murmur is often audible over the pulmonic orifice and moderate pulmonary emphysema may be found Clubbing of the fingers is common Congestive heart failure with hepatomegaly edema and ascites appear early Ordinarily the disease runs a rapid course after the appearance of symptoms Frequent phlebotomy with the removal of relatively small amounts of blood (200 ml) may afford some symptomatic relief

Sclerosis of small pulmonary arteries due to stasis (secondary sclerosis) is a common event when the pulmonary vessels are engorged for a long time The small precapillary arteries are involved in the same way the peripheral arterioles are affected in systemic hypertension This sclerosis is common in rheumatic mitral stenosis It also develops regularly although in varying degree in other conditions associated with increased pressure in the lesser circuit these conditions

are exemplified by congenital heart lesions emphysema kyphoscoliosis fibrotic pulmonary tuberculosis and extensive pleural adhesions

The etiologic significance of elevated pressure in the lesser circuit for the development of pulmonary atherosclerosis is emphasized by the readiness with which this lesion develops in childhood when transposition of the large vessels patent ductus arteriosus or a defect in the interventricular septum create an abnormally high pressure in the lesser circuit

Hypostatic Congestion and Pneumonia

In debilitated patients who do not change their position for a long time and who do have congestive heart failure hypostatic congestion develops in the dependent parts of the lungs Sudden infiltration and pneumonia may develop in these areas Hypostatic pneumonia is often diagnosed when pulmonary embolism with infarction exists

Increased Basal Metabolism

An increased basal metabolic rate so often found in patients with cardiac failure is due to the dyspnea the increased temperature intake of more oxygen because of tissue anoxia excitement and other unknown factors

Mental Disturbances

Insomnia a mild depression or greater irritability are common in heart failure particularly in the presence of Cheyne Stokes breathing Delirium mental confusion hallucinations may occur Cerebral edema is in part responsible

Fatigue

Marked fatigue is a common symptom in cardiac patients and particularly among those with arteriosclerosis Often it is the only complaint Sometimes this symptom stems from a diminished intake of thiamine in which case it is easily treated In patients who have been on a salt free diet for a long time the fatigue is the result of sodium chloride deprivation Sometimes it is a symptom of an anxiety neurosis A diminished content of potassium in the skeletal muscle has been held responsible In many cases digitalis therapy may help and it is probable that tissue anoxia due to the lowered cardiac output is an etiologic factor In most cases however no reason for the fatigue is found and the symptom often vanishes after having been present for months with no change in the objective findings

Hepatic Enlargement

Engorgement of the liver is properly regarded as the earliest sign of right heart failure The liver is located directly upstream from the right heart and is separated from the inferior vena cava and right atrium only by the wide valveless

hepatic veins The left lobe of the liver seems to enlarge first in cardiac patients probably owing to the anatomic arrangement of the hepatic veins and their branches For this reason patients with hepatic engorgement rarely complain of pain in the right side of the abdomen Instead relief from stomach pain is sought since the distress is felt in the epigastrium Some time may elapse before it is realized that swelling of the liver and not a gastric disorder is responsible for the pain

At first this pain may be experienced only after meals which tends to confirm the patient s opinion that it is of a gastric origin Sometimes it occurs only on exertion (Boyer and White)

Not every congested liver causes pain or is tender on palpation Congestion frequently enlarges the liver so much that the upper portion of the right abdomen bulges although the patient reports nothing more than epigastric fullness no pain is elicited by pressure or palpation In such cases the congestion is slow in onset or of long duration The more acutely right heart failure develops the more marked is hepatic pain Therefore both the presence or absence of pain and tenderness on pressure in the hepatic area are valuable means of appraising the speed with which right heart failure develops or its duration If an already enlarged liver again becomes sensitive on pressure progressive right heart failure is present even if no other signs support this conclusion For the reasons mentioned the gradual development of hepatomegaly in pericardial adhesions precludes sensitivity of the liver On the other hand the hepatic engorgement resulting from paroxysmal tachycardia (paroxysmal fibrillation) or right heart failure from pulmonary embolism develops acutely producing pain and tenderness of the liver on palpation

The pain from an acute hepatic engorgement is not felt exclusively over the liver it may radiate to the right shoulder and be mistaken for arthralgia

Meteorism and nausea appear in many cases of hepatic congestion an increased excretion of urobilinogen and urobilin are regular findings The stasis gastritis aggravates the symptoms The distention of the intestines increases the abdominal pressure and decreases the venous backflow and thus may enhance edema formation

Vomiting is a common manifestation of acute hepatic engorgement and presumably is the result of peritoneal irritation The ominous vomiting that occurs in patients with diphtheria and acute heart failure as well as that appearing in patients with paroxysmal tachycardia is a well known phenomenon Hepatic enlargement and vomiting is not infrequent in patients who receive digitalis in small amounts Indeed the physician often ascribes the vomiting to this drug and discontinues it but the fact is that the vomiting ceases quickly if increased amounts of digitalis are administered since this symptom results from progressive heart failure

Enlargement of the liver may be seen in right heart failure at a time when the venous pressure is still not yet increased this is explained by the fact that the hepatic veins flow into the inferior vena cava at an angle of almost 90 degrees

thus producing an early congestion that would not be produced were the angle less than 90°

The retention of approximately 1500 ml of blood in a congested liver and the consequent withdrawal of this amount from the circulation may cause pulmonary congestion to diminish and dyspnea as well as cyanosis to disappear

Histologically the congested liver shows a typical widening of the central vein with necrosis of the central cells This seems to be caused by hypoxia because this portion of the liver lobule receives less oxygen

Heart failure with chronic hepatic congestion is claimed to be responsible for attacks of hypoglycemia with sudden weakness sweating palpitation and nervousness Psychoses convulsions and coma may also appear As the result of congestion a nutmeg liver may develop and the amount of fibrotic tissue may gradually increase in the central part of the lobule This increase was found in one third of 286 cases of chronic passive congestion of the liver Congestive cirrhosis with splenomegaly gradually develops In recent years this has become a more common finding since mercurial diuretics prolong the life of these patients for years formerly death occurred before congestive cirrhosis of the liver could develop

Liver function in patients with congestive heart failure may be disturbed Direct and indirect bilirubin in the serum is raised in heart failure corresponding to the degree of liver congestion Different tests of hepatic function show abnormalities such as the tendency to lower albumin and greater globulin levels in the serum

Congestion of the intestinal tract in patients with engorgement of the liver leads to meteorism eructations and the sensation of fullness The meteorism is due to diminished reabsorption of gases caused by venous congestion (Schoen)

JAUNDICE

The skin and sclera may become slightly yellow (subicteric tint) in patients with congestive heart failure and evident hepatic congestion Jaundice appears because the pulmonary congestion is associated with destruction of many red blood cells while the liver damage in right heart failure the result of hypoxia impairs its excretory function If jaundice becomes pronounced pulmonary infarction should always be suspected

Large amounts of urobilin and urobilinogen and even (rarely) bilirubin may be excreted in the urine The van den Bergh reaction in the blood serum is usually delayed and indirect as in hemolytic jaundice of other origin but a direct reaction may be obtained with greater liver damage

If the patient has edema jaundice may be absent from the edematous areas

EDEMA

The formation of edema in most cardiac patients is the result of multiple rather than single factors While a marked alteration of one of the mechanisms about to be described may be provocative usually a number of abnormal con

ditions interact to produce edema (In this respect one is reminded of the mechanism of dyspnea)

The movement of water through the capillary wall into the tissues depends mainly upon the intravascular (hydrostatic) pressure the centrifugal force which drives water into the tissue and the colloidosmotic (oncotic) pressure of the plasma proteins as the major opposing force which tends to retain water within the vessels Both of these factors in turn are opposed by the hydrostatic and colloidosmotic pressure of the tissue fluids

Normally the forces are so balanced that the quantity of fluid pressed through the capillary membrane into the tissue equals the amount removed by the lymphatics or discharged back into the capillaries Three factors were formerly held responsible

Increased Venous Pressure Under normal conditions the hydrostatic pressure in the arterial section of the capillaries is higher than all opposing forces and therefore plasma passes into the tissue spaces Since this hydrostatic pressure is lower in the venous limb of the capillary fluid passes from the tissues to the capillary in this area This mechanism is altered if venous pressure is increased A high venous pressure also impedes the flow of lymph because the entrance of lymph into the large veins in the upper thorax will be retarded as well Mechanical compression of veins causes edema The amount of edema however does not parallel the height of venous pressure Even ligation of the inferior vena cava frequently does not result in the formation of edema

While other factors are of greater importance venous engorgement has importance in the formation of edema This mechanism explains why edema of cardiac patients is dependent and collects at points where venous pressure is particularly high It also makes clear why patients with pericardial adhesions and inflow stasis due to compression of the superior vena cava have facial edema only when in the supine position Their edema disappears in the erect posture because of the consequent lowering of pressure in the tributaries of the superior vena cava

Increased Permeability of the Capillary Endothelium If the circulation is disturbed and the oxygen supply to the tissues diminished the capillaries may become more permeable to water and crystalloids The development of tissue anoxia is enhanced by the increased oxygen requirements of the tissues (increased basal metabolic rate) in decompensated cardiac patients However the low protein content of the edema fluid and the absence of hemoconcentration in acute heart failure with edema formation show that this factor is not solely responsible With severe anoxia in patients with pulmonary diseases and congenital heart lesions edema is often absent

Hypoproteinemia Cardiac patients often have a relatively low level of serum proteins as the result of several factors such as the great loss of albumin in the urine when renal congestion is present Hypoproteinemia may also stem from malnutrition Great loss of proteins also occurs in conjunction with edema and transudates This loss of protein may be great if hydrothorax and ascites develop

and their evacuation by paracentesis is necessary If the critical level of plasma proteins is reached (5 5 Gm of plasma proteins with 2 5 Gm of plasma albumin per 100 ml of plasma) edema appears occasionally The oncotic pressure of the serum is diminished in cardiac patients even before edema forms The serum *protein level is said to fall in right but not in left heart failure (Kagan)*

Other Causes The pathogenesis of diffuse and circumscribed edemas which appear in women suffering from climacteric disturbances or during the menstrual period is obscure It is most probably connected with the retention of sodium caused by the sex hormones Injection of crystalline preparations of estrone progesterone and pregnandiol causes water sodium and chloride retention in normal dogs (Thorn et al) Similar retention is observed premenstrually in humans these substances are excreted in increased amounts at the beginning of menstruation Such patients suffer from headaches fatigue vertigo and even mental aberration

New Concepts of the Mechanism of Edema

In acute hemorrhage and in certain types of shock a widespread vasoconstriction occurs this has been claimed to be a useful phenomenon (by addicts of teleologic reasoning) because it diverts blood from less vital organs to more important ones — the heart brain and kidney The arteries of these organs were said not to participate in the general vasoconstriction In recent years it has become increasingly clear that this concept is fallacious Attacks of sudden blindness that have been observed after acute hemorrhage indicate participation of the retinal arteries in the general vasospasm We were able to show that marked electrocardiographic changes appear temporarily in a majority of patients with acute hemorrhage thus demonstrating the participation of the coronary arteries Experimental investigations and the finding of azotemia following a profuse hemorrhage show that a reduction of renal circulation also exists in these patients

Patients with cardiac failure respond in a similar manner as those with in acute hemorrhage Here also — as pointed out earlier — general vasoconstriction takes place as a consequence of the diminution of cardiac output However while in other organs the diminished blood supply parallels and corresponds to the diminution of cardiac output renal blood flow is reduced out of all proportion If the cardiac output is reduced to one half its normal value renal blood flow is reduced to 20—30 per cent of normal which in turn causes a reduction of the filtration rate in the kidney to 50—75 per cent of normal This is said to be accomplished by the constriction of the efferent and according to some investigators the afferent glomerular arterioles The mechanism of the event is still not clear Tubular function seems to be unchanged while owing to the presence of diminished filtration rate with normal reabsorption in the tubuli more sodium and consequently more water is retained According to others (Davies and Kilpatrick Sinclair Smith and others) the tubular absorption of sodium is actually increased

Thus a response which is useful in acute hemorrhage — to a degree — for the preservation of the species by conserving electrolytes and fluids and by lessen

ing their excretion through the kidneys leads in heart failure to the formation of edema

According to Starling s rules of equilibrium (see p 83) cardiac failure leads to increased venous and capillary pressure This causes the transudation of fluid (edema) The consequent reduction of plasma volume causes retention of salt and water According to the new conception cardiac failure causes via the renal mechanisms just mentioned retention of salt and water the plasma volume expands the venous and capillary pressures rise and transudation into the tissues takes place

The new conception lacks universal approval The necessity of accepting Starling s rules of osmotic and hydrostatic equilibrium is stressed (Peters) and so is the important part which the increase of venous pressure plays in edema formation According to some authors (Miller) the initial phenomenon is retention of water sodium being retained secondarily For many years the discussion has been going on whether venous pressure must rise before edema appears (Jouve and Vague) The experiments of Starr in which it was demonstrated that in resting dogs very severe damage of the right ventricle by burning need not cause a conspicuous increase of venous pressure do not prove too much since increased venous pressure would in all probability have been found had the dogs been forced to work In patients with severe acute myocardial infarction following coronary occlusion we see no congestion unless heavier meals or physical exertion increase the amount of circulating blood The venous bed is wide and can be expanded the venous pressure need not rise immediately therefore when right ventricular failure appears

The participation and the degree of action of hormones from the adrenal cortex and hypophysis in edema formation has not been elucidated It may be assumed that these hormones control the excretion of sodium and water (Raab Singer and Wener Bornstein Hanenson et al) Raab elicited the clinical picture of congestive heart failure by overdosage with adrenocorticotropic hormone

The part played by the antidiuretic hormone of the hypophysis and the sodium retaining corticoid aldosterone is under active investigation The excretion of aldosterone in the urine is markedly increased in heart patients with cardiac failure and edema A temporary increase is also seen in patients with acute myocardial infarction (Wolff)

An inadequate cardiac output causes a discharge of adrenocortical hormone and a discharge of posterior pituitary hormone The hormonal action on tubular reabsorption of salt and water may thus play a paramount part in the formation of edema in cardiac failure (see Hamilton)

While the finer mechanism of the diminution of the renal excretion of sodium and water is unknown there is no doubt that renal blood flow is diminished in cardiac failure These investigations were significant since physicians were again led to realize the importance of sodium in the genesis of edema a point stressed by Widal and others more than 50 years ago

The early recognition of water retention is very difficult When edema becomes visible and when pitting appears a considerable amount of water has already been retained in the body about 5 to 6 kilograms are retained before pitting is demonstrable Edema can be detected by palpation if the size of the limb has increased 8 to 10 per cent Accordingly an accurate record of the patient s weight is the most reliable simple method of following water balance when retention is suspected or discovery of recurring edema is important Several tests have been advocated for early diagnosis of water retention but they are not reliable and for the most part have been abandoned

In elderly as well as in obese patients edema often appears in the absence of demonstrable cardiac damage It is a common event during periods of continued warm weather Individuals who stand quietly without moving their legs may develop ankle edema Edema appearing in only one lower extremity is not of cardiac origin superficial or deep varices or deformities of the foot (fallen arches and the like) are more likely causes

If the skin becomes wrinkled over an edematous area the edema is receding provided no alteration of position has occurred

The edema may be hard or soft Hard edema is usually chronic and exhibits changes in the connective tissue Occasionally this type — which may be painful — is found in the abdominal wall but rarely above the level of the umbilicus Thrombosis of the deep veins of the abdominal wall apparently is the major etiologic factor

Sometimes bilateral edema of the hands and arms appears in very advanced heart failure when venous pressure is markedly raised Unilateral edema of an arm may develop in this stage if the patient has increased local venous pressure brought about by lying on the affected side Thrombosis of the jugular vein causes unilateral edema of the arm the face and the breast on the corresponding side If the superficial vessels of the neck become thrombosed the jugular veins may be palpable as hard cords

Massive edema and necrosis of the toes and occasionally also of the ear and tip of the nose have been observed in connection with ball thrombi of the left atrium (see later)

When the patient is confined to bed the examination should include inspection and palpation of the sacral region for cardiac edema is a gravity edema and collects in the most dependent part

There is no parallelism between the severity of the decompensation and the degree of edema This must be anticipated since the edema is usually the result of an interplay between several mechanisms

HYDROTHORAX

One of the earliest signs of decompensation that often antedates all other evidence of cardiac failure by months is hydrothorax

In most cardiac patients hydrothorax is more prominent on the right side It may be absent on the left side even when a massive effusion exists on the right

It has been maintained recently that a right sided effusion appears most commonly in patients with mitral lesions in combined left and right heart failure and in atrial fibrillation whereas a left sided effusion is more common in patients with left ventricular failure An enlarged left ventricle is alleged by compression to impede the circulation in the left pulmonary veins while a dilated right atrium hampers the return from the right pulmonary veins Exceptions to these rules are by no means uncommon and in our opinion right sided effusion is the rule, irrespective of the etiology of the heart failure

Very often the appearance of a right hydrothorax follows infarction in the middle or lower lobe of the right lung Infarction in the left lung may cause a left sided effusion If the right pleural cavity is obliterated by adhesions and the conditions prevail in which a hydrothorax develops the effusion can form only on the left side Right pleural adhesions are common in cardiac patients with chronic failure due to repeated pulmonary infarction Left sided effusions sometimes develop after coronary thrombosis

Many hypotheses have been devised to explain the high incidence of effusions into the right pleural cavity Some of these theories assume that an enlarged right atrium compresses the azygos vein or that differences of intrathoracic pressure play a role It has al o been stated that the average venous pulmonic pressure is higher in the right lung especially with the patient in the preferred right recumbent posture The pulmonary venous blood from the right lung must be lifted more than that from the left lung to reach the left atrium (Dock) The volume of the right lung seems to be 10 per cent larger than that of the left This makes the surface exuding fluid larger Convincing proof to support either explanation however is lacking

Hydrothorax may develop in right or left heart failure The veins of the parietal pleura drain for the most part into the azygos system whereas the veins of the visceral pleura send their blood mainly into the pulmonary veins Therefore increase of pressure in either atrium may lead to edema Pulmonary engorgement seems to be the chief factor in the development of hydrothorax

Bilateral hydrothorax is an early and rather regular phenomenon in acute hemorrhagic nephritis and is indicative of the general capillary damage in this condition

When hydrothorax persists for some time (it may last for years) its protein content may be relatively high so that the differential diagnosis between an exudate and transudate is impossible by the usual laboratory tests

X ray permits an earlier diagnosis of hydrothorax than does physical examination since a considerable amount of fluid at least 500 ml must collect in the pleural cavity before physical examination will disclose it Moreover x ray examination is invaluable for the diagnosis of interlobar effusions which are not uncommon on the right side when adhesions have been created by previous pulmonary infarctions It should be emphasized however that the fibrotic tissue of pleural adhesions may become so edematous that a differential diagnosis by x ray between edematous adhesions and a free hydrothorax is difficult This

difficulty becomes more comprehensible when one recalls that free pleural effusions usually develop first along the visceral pleura and therefore cause x ray findings which resemble pleural adhesions

If a massive hydrothorax is added to the pulmonary congestion and to the enlarged heart the vital capacity is markedly reduced for mechanical reasons the resultant cyanosis and dyspnea may be very pronounced

ASCITES

If ascites dominates the clinical picture severe passive congestion in the portal circulation should be suspected Under these circumstances two conditions deserve serious consideration First tricuspid insufficiency may be present usually this is easily recognized by the expansile pulsation of the liver and the positive venous pulse in the neck Second the inferior vena cava or hepatic veins may be compressed by adhesions at the base of the right lung or by pericardial adhesions In many patients the thin walled hepatic veins empty into the inferior vena cava in part or entirely above the diaphragm Consequently they are readily compressed by a pericardial effusion or adhesions in this region Ascites may however also appear in conditions other than tricuspid and pericardial lesions e g occasionally in syphilitic aortic regurgitation

It is of practical importance to note that effusions in the pleural and peritoneal cavities are continuously absorbed and reformed It has been estimated that 40 to 80 per cent of the ascitic fluid enters and leaves the abdominal cavity per hour[1] The appearance of ascites is based upon the fact that the outpouring of lymph into the peritoneal cavity continuously exceeds normal In ascites reabsorption is affected by the venous congestion This continuous circulation of the effusion in the pleural and abdominal cavities explains the diuretic effect that follows the injection of mercurial diuretics into ascitic fluid or into a hydrothorax

RENAL CONGESTION

Congestion of the kidneys produces changes in the urine which are often characteristic The urine is concentrated and the specific gravity may be as high as 1 035 If allowed to stand a few hours after it is voided the urine is dark red in color because of the presence of large amounts of urobilin Albuminuria is usually present and may be pronounced The number of granular casts likewise increases There may be 10 times as many red blood cells as in the urine of a healthy individual

The discovery of a marked albuminuria in conjunction with casts and increased number of red blood cells in the urinary sediment may create the wrong impression of a primary renal lesion especially when the blood pressure is high The great increase in the specific gravity of the urine and its high content of urobilin and urobilinogen speak in favor of renal congestion

Many tests have been introduced for the evaluation of renal function The simplest and best is one of the modifications of Volhard s dilution and concen

tration test An amount of 1000—1500 ml of water is taken and one observes whether this fluid is excreted within four hours During the day the patient is not allowed any fluid and the specific gravity of the urine should gradually rise to values above 1 025 in the healthy It should be stressed that this test is applicable for the determination of renal function only when there is no evidence of congestive heart failure If the latter is present or imminent retention of the ingested water is marked and abnormal values of the urinary specific gravity are obtained

The blood nonprotein nitrogen and urea may be abnormally high in congestive heart failure or following myocardial infarction The values return to normal soon after improvement begins In such cases some intrinsic renal lesion like atherosclerosis or arteriolosclerosis is often present in addition to congestive heart failure While the renal lesion does not suffice to create any disturbance it causes azotemia as soon as some circulatory disturbance is superimposed Precipitous fall of blood pressure in myocardial infarction leads to azotemia by the same mechanism as in acute blood loss that is narrowing of the arterial tree particularly in the kidneys Nonprotein nitrogen may also increase as the result of too energetic treatment with mercurial diuretics in an attempt to relieve edema

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Chapter 6

The Circulation Time

THE VELOCITY OF BLOOD FLOW is ascertained by measuring the so called circulation time In clinical medicine the circulation time is found by introducing some substance into the circulation and determining the time required for its arrival in sufficient quantities at another point to produce either an objective response or a response determined by other methods

Substances Used Many substances have been suggested among which may be mentioned ether lobeline sodium cyanide aminophyllin fluorescein saccharine histamine calcium chloride radium magnesium sulphate sodium dehydrocholate labeled erythrocytes calcium gluconate sodium succinate methylene blue and congo red Some of these substances possess the advantage of giving responses that are amenable to objective observation

Methods and Normal Values Ordinarily the circulation time is measured from the moment of injection to the appearance of the substance in the skin tongue carotid sinus an artery of the opposite arm etc Even when the test is performed with great care and with the patient under basal conditions the values for normal circulation vary The normal arm to skin time varies from 9 to 20 seconds according to the method used The injected substance naturally appears earlier in the arm than in the leg (approximately half the time)

The arm to lung circulation time is measured with the aid of ether Ether (0 2)—0 33 ml) and saline (0 5) ml are injected intravenously and a cough deep breath or the smell of ether on the breath is considered the subjective and objective endpoint Other substances have also been used — paraldehyde for example also elicits a cough reflex Arm lung times of four to eight seconds are considered normal

With a combination of these methods i e by measuring the arm to lung and the arm to tongue time it is possible to calculate the lung to tongue time or the velocity from the lung to some part of the systemic circulation

The circulation time is greater when the blood volume is increased and shorter when the cardiac output rises Cardiac output is increased with higher room temperature It may rise 40 per cent after a meal and 100 per cent during anxiety

Of great importance is the discovery by Nylin and his collaborators that in dilated hearts the circulation time is prolonged because the injected substance is mixed with the enormously increased residual blood in the dilated cardiac chambers Under normal conditions the heart has a capacity of 400 ml The heart

of a patient with aortic insufficiency may have a capacity of 3000 ml and the amount of residual blood may exceed 2000 ml Therefore in patients with enlarged heart an increased circulation time does not necessarily indicate a slower blood flow

To obtain a reliable test the physician should have the patient rest comfortably for at least 20 minutes before the test is taken

Interpretation Since the speed of the blood flow in the arterial part of the circulation (pulmonary artery and its tree aorta and its vascular branches) is not remarkably altered even in advanced heart failure prolongation of the arm to lung circulation indicates a delay in the flow in the systemic veins in right heart failure In heart failure the figures for arm to skin and arm to lung circulation may be trebled With a normal arm to lung circulation time prolongation of the arm to tongue circulation time indicates a delay in the pulmonary veins caused by left heart failure

The circulation time is decreased in beriberi anemia fever and hyperthyroidism It is also shortened in arteriovenous fistulas and in congenital heart disease with a right to left shunt It is increased in myxedema

The values of circulation time do not parallel the degree of heart failure The range of errors in the performance of the test must be considered Moreover heart failure may be present even though the circulation time is normal or the circulation time may be prolonged when the patient is relatively free from symptoms Improvement may result from therapy while the circulation time remains unchanged For these reasons as well as because of the variations encountered in healthy subjects most of these procedures have limited practical importance in bedside cardiology Furthermore diagnosis of congestive heart failure is easier and no less exact by other means Since healthy subjects show a wide difference in the velocity of circulation the method does not permit the diagnosis of beginning or imminent heart failure

The procedure has some value however in the recognition of right to left shunts in congenital heart disease in the differentiation of bronchial and cardiac asthma (the circulation rate in the former is normal) in the localization of pericardial adhesions which compress the superior or inferior vena cava in the evaluation of how much the heart contributes to dyspnea in a patient with pulmonary emphysema and cardiac disease (pulmonary emphysema does not prolong the circulation time) and in ascertaining whether ascites is the result of cardiac failure Of theoretical interest also is the discovery of the diminished velocity of blood flow in most patients with congestive heart failure

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Chapter 7

Venous Pressure

THE CLINICAL IMPORTANCE of venous pressure became fully appreciated when it was realized that cardiac activity depends to a considerable extent upon the amount of blood returned to the heart, and that this in turn depends upon the venous pressure. The veins cannot be regarded as passive tubes; their width and capacity vary continually under the influence of hormones, chemical substances such as carbon dioxide, and central and reflex (carotid sinus) nerve impulses. It is the amount of blood returning to the heart which regulates the cardiac output, rather than the converse. If the quantity of blood returning to the right heart is greater than the heart can transfer to the arterial side, venous pressure rises. Normally, venous pressure rises during exertion.

Measurement of venous pressure aids in the clinical diagnosis of right ventricular failure. Moreover, it will often help to determine whether cardiac decompensation plays a part in a case of hepatic enlargement or ascites. Likewise, determination of the venous pressure will often make it possible to learn how much the cardiac factors contribute to the clinical picture when a patient has extensive pulmonary emphysema and fibrosis.

In some cases of right ventricular failure, however, the liver may be enlarged and edema present while venous pressure is normal. In these cases the veins may be dilated, so that inspection sometimes yields more information than the determination of venous pressure, since the venous bed has adapted itself to the greater content.

Methods. Whereas a dilated vein which is not under pressure is difficult to palpate, a marked increase in venous pressure causes it to feel like a hard cord or a thrombosed vessel.

The simplest method for determining venous pressure remains the procedure originally suggested by Gaertner. This method is based on the fact that since the veins of the upper extremities communicate with the right atrium, they act like a manometer and indicate intra-atrial pressure with great exactitude. If the arm of a relaxed and seated patient is permitted to hang down for 15 minutes, the veins on the back of the hand become congested and easily visible. If the eyes of the examiner are fixed upon a small vein on the back of the hand and the arm of the patient is slowly elevated by the observer, a point will be reached at which the pressure in the hand vein exceeds the pressure in the right atrium; at this moment the vein empties and collapses. The level at which this collapse occurs is regarded as the point at which the vein is subject to the same pressure as the right atrium.

As a reference point the upper border of the fifth rib is chosen in the seated patient Normally the veins should collapse 10 cm above the reference point Sclerotic veins however do not collapse readily The observation that the venous pressure in one arm may be higher than in the other if the first has performed some work shortly prior to the test demonstrates that the values obtained with this method do not depend upon the state of the circulation alone

Sir Thomas Lewis recommended inspection of the superficial jugular veins for the estimation of venous pressure Normally these veins collapse if they are flush with the upper end of the manubrium sterni This is the reference level regardless of body position Therefore in the upright posture no portion of the vein should be visibly congested under normal conditions If the veins remain engorged above this level venous pressure is elevated and the higher this congestion extends up the neck in the erect patient the higher the pressure

As a reference level in the supine position some observers recommend a point 5 cm dorsad to the fourth costochondral junction or 10 cm above the level of the back of a patient lying on a table

The normal levels vary according to the reference point used and range from 4 to 15 cm water Some investigators regard 10 cm as the upper limit and others consider values over 15 cm as abnormal Figures of over 32 cm have been obtained in congestive heart failure Direct measurement of the pressure by means of a catheter within the human right atrium yields values of 3 to 7 cm water in normal persons

A needle introduced into a vein provides a direct method for measurement of venous pressure but this technic also suffers because of the impossibility of locating the correct zero level This and other similar methods offer little advantage over the procedures mentioned above

Interpretation While there is no parallelism between the height of the venous pressure and the degree of decompensation venous pressure is usually elevated in failure Since venous pressure is normal in uncomplicated emphysema and lung asthma this fact may aid in problems of differential diagnosis It is elevated in a compensated tricuspid stenosis and in pericardial adhesions The method is of value in the diagnosis of obstruction of the superior or inferior vena cava Following venesection venous (and spinal fluid) pressures fall

Within certain limits increased venous pressure means better filling of the heart and therefore improved cardiac efficiency in accordance with Starling s law this holds true despite the shortening of diastole by the increase of heart rate via the Bainbridge reflex In this sense it helps to compensate the heart lesion These rules are not valid when the heart has no reserve force

Of clinical interest is the phenomenon of *hepato jugular reflux* Strong pressure exerted with both hand on the right upper abdomen particularly on the patient s liver area does not change the filling of the veins of the neck in normal individuals The venous pressure remains unchanged or more often it falls 1 to 3 cm water In patients with right heart failure the veins become engorged and the venous pressure may rise by 3 cm water According to Burch and Ray increased tonus of the veins in conjunction with greater filling is responsible

of 3500 postmortem examinations but by using a more exact procedure the same authors found the condition in 14 per cent of the cases in a second series of patients (Hampton and Castleman) There is no other autopsy finding which is more readily passed over In many reports only the number of infarctions is noted the fact that pulmonary embolism often is not followed by infarction finding no consideration Whereas Belt believes that infarction occurs in somewhat more than 50 per cent of the cases of pulmonary embolism others found an infarction only in 27 to 30 per cent In another study in which pulmonary infarction was observed in 5 2 per cent of 6 348 necropsies only 22 per cent of these infarctions were diagnosed ante mortem In 60 per cent a medical disease existed (Krause and Chester) It is claimed that a pulmonary embolism appears after 3 5 per cent of major operations and in 5 3 per cent of parturitions At least every tenth embolism is said to be lethal but we would assume the incidence of death to be much rarer The danger of pulmonary embolism is greater in all patients over 50 years old especially if they are obese It is estimated that 34 000 persons in the United States die every year from this accident Fat embolism occurs after injuries Air embolism is prone to occur in connection with fractures Embolism from tumor particles is rare but does occur

Fatal pulmonary embolism may rarely develop from a thrombus in the axillary veins following diagnostic or therapeutic venipuncture

Pathology

Pulmonary Embolism Embolism may occur in the trunk of the pulmonary artery in one of its main branches or in its peripheral ramifications In a majority of instances the embolus lodges in a vessel supplying the lower lobe of the right lung This is not entirely explained by anatomic factors such as the greater width of the right pulmonary artery The location of pulmonary infarcts was recorded in a series of 200 cases with the following result 84 cases had infarction of the lower lobe of the right lung 52 showed an infarction of the lower lobe on the left 64 had infarction of both lungs (Gsell) According to the same observer infarction of an upper lobe occurs in only 10 per cent of the cases and these have a poorer prognosis Multiple rather than solitary pulmonary embolism characterizes a high percentage of cases a point of major therapeutic import

If small masses of a radiopaque substance are introduced experimentally into the femoral vein of a dog a majority of such emboli pass into the branch of the pulmonary artery supplying the lower lobe of the right lung in two experiments three out of every five emboli inserted in this way even passed into the same small artery of the right lower lobe (Scherf and Schoenbrunner)

Pulmonary Thrombosis Hemorrhagic infarction of the lung may also be the consequence of thrombosis of a pulmonary artery Fowler found thrombosis of this vessel 6 times in 935 consecutive necropsies A distinction between pulmonary thrombosis and pulmonary embolism may be difficult even at necropsy The formation of a thrombus at the site of a small embolus is also encountered A part of

the thrombus may become detached and may cause an embolism in a peripheral part of the artery Often a thrombus forms at the site of sclerosis of a pulmonary artery Pulmonary thrombosis is also encountered in the postoperative or post partum period and is common in conjunction with disease of the pulmonary or mitral valve Since such thrombi ordinarily are terminal developments the symptomatology tends to be masked by the underlying disorder Dyspnea and cyanosis stand in the foreground of the clinical picture while the stormy mani festations of pulmonary embolism are often absent

Pulmonary Infarction Since pulmonary embolism often is not followed by hemorrhagic infarction an accurate postmortem estimate of its incidence would require a technic similar to that used to discover coronary occlusion namely radioscopic examination after the injection of an opaque substance into the pulmonary artery The formation of a hemorrhagic infarct is greatly enhanced by the presence of pulmonary congestion this may account for the high incidence in cardiac patients In the experimental animal hemorrhagic infarcts appear after ligation of the pulmonary arteries *and* veins

Hemorrhagic infarction of the lung may have other causes Thus infected emboli formed in the course of a general sepsis cause capillary damage and hemorr hagic infarction Embolism of a large pulmonary artery or embolism in old people causes hemorrhagic pulmonary infarction Anemic infarction of the lung is un common

Pulmonary embolism leads to localized hyperemia and edema The hemorr hagic infarct is a solid well defined conical mass whose apex extends toward the hilus The base of the infarct is almost invariably formed by the pleura so that pleural irritation is inevitable Around the infarct is a zone of reactive inflam mation just as it develops in the myocardium after infarction The alveoli are filled with blood which may be fresh or disintegrated depending upon the age of the infarct Unlike a cerebral apoplexy the pulmonary parenchyma is not destroyed by a hemorrhagic infarct and the red blood cells are slowly absorbed If the patient survives there may be complete healing without evidence of necros is and the site of a former infarction may be visible on x ray films only as a fine scar a small pleural adhesion may be the sole evidence of a previous pulmo nary infarction

Hemorrhagic infarctions heal slowly Eighteen months may be required before canalization is complete or the scar forms Encapsulation and cicatrization are not unusual but the formation of pulmonary cysts after infarction is rare If the patient survives embolism of a large pulmonary artery canalization may follow The ensuing arterial stenosis may lead to secondary thrombosis

Symptom

Massive and Small Embolisms Occlusion of the main stem of the pulmonary artery by an embolus causes almost instantaneous death and scarcely requires detailed comment Sometimes the patient has only time to cry out in alarm If

death is delayed for a few minutes the syndrome of sudden asphyxia marked anxiety cyanosis and finally loss of consciousness is most dramatic

Massive embolism of one large pulmonary artery multiple embolisms of smaller vessels or a solitary embolism of a small peripheral lung artery may produce a very similar picture Accordingly one should not infer that massive embolism has occured merely because the subjective phenomena are severe As a matter of fact even massive pulmonary embolism causes remarkably few symptoms at times This is understandable since the clinical picture in most cases does not derive from the mechanical obstruction of the pulmonary vessels

Dyspnea One of the most common symptoms is dyspnea of sudden onset It may be mild or extreme — in the latter instance it requires immediate treatment The sudden occurrence of dyspnea in a cardiac patient particularly a bed ridden one arouses the suspicion of a pulmonary embolus provided no other explanation is satisfactory This dyspnea is subjective and objective Breathing is rapid often shallow and is associated with great apprehension or even extreme anxiety For the most part the dyspnea is of reflex origin but massive embolism will cause dyspnea without the activation of reflexes Pulmonary edema occasionally occurs and causes dyspnea Dyspnea may be the only symptom of pulmonary embolism Experimentally it occurs even when small arteries are occluded and disappears immediately if the vagi are severed If reflex bronchospasm develops as occasionally happens the breathing may be asthmatic

Pain Pain is a common symptom of pulmonary embolism Four types can be distinguished

(1) Pain may be felt in the precordium or in the retrosternal area and may present all the features of pain from a myocardial infarction The pain may be mild or excruciating it may last for hours and like the pain of coronary occlusion it may radiate into the arms As will be shown later the distinction between pulmonary embolism and myocardial infarction may be extremely difficult In a series of 100 cases of the former there was a history of pain in 32 instances In another report pain in the chest or back was mentioned in 50 per cent of the cases (Moller) This pain may occur without any changes appearing in the electrocardiogram At least in some patients this pain may be due to a similar mechanism as that observed in patients with high pressure in the lesser circuit (see chapter on Cor pulmonale)

(2) Sometimes anginal pains recur at short or long intervals during the first twenty four hours The pain experienced may last for only a few minutes and may radiate to the ulnar side of the left or right arm Nitroglycerin brings prompt relief (Scherf Currens and Barnes)

(3) Hours or days after pulmonary embolism pain may develop in the right or left side of the chest It is aggravated by deep breathing The pain is typical of pleuritis this diagnosis being confirmed by the appearance of a friction rub over the involved area

(4) A constant pain may be referred to the shoulder neck abdomen or lumbar region It lasts usually for days The common occurrence of this kind of pain and the frequency with which it is misinterpreted is worthy of emphasis Presumably the pain results from diaphragmatic pleurisy The great incidence of pulmonary infarction at the base of the right or left lung makes irritation of the diaphragmatic pleura a common event The center of each leaf of the diaphragm is innervated by the phrenic nerve which is derived from the cervical segments inflammation of the dome of the diaphragm therefore causes pain which is referred to the cervical region Experimental irritation of the central portion of the diaphragm actually causes pain which is referred to the neck and shoulder corresponding to the third and fourth cervical segments (Capps and Coleman) These patients are often treated for arthritis Likewise after gynecologic operations the pain is falsely attributed to the pressure of shoulder pads while the patient is in the Trendelenburg position Since the costal or marginal portion of the diaphragm receives afferent nerves from the last six thoracic nerves irritation of this section evokes pain that seems to arise in the lower part of the thorax the upper abdomen or the lumbar region

For this reason patients with pulmonary infarction may be suspected of acute appendicitis or cholecystitis and as personal experience has repeatedly confirmed this has often led to unnecessary laparotomy Since strong stimuli cause muscular rigidity tenderness and hyperesthesia of the corresponding segments the danger of an erroneous diagnosis is great

Irradiation of pain to other segments and even to the opposite side may occur If autonomic stimuli irradiate reflex visceral spasm and even paralytic ileus may develop in connection with pulmonary embolism (see next chapter)

Sometimes pain is felt later over the precordium when pericarditis supervenes (see below)

Hemoptysis The diagnostic importance of hemoptysis in pulmonary embolism is overestimated for it actually occurs only in a minority of cases Hemorrhagic sputum cannot occur unless a hemorrhagic infarct develops and is infrequent even when necropsy discloses several old and recent hemorrhagic infarctions When present hemoptysis undoubtedly facilitates the diagnosis Sometimes only close inspection of the sputum reveals the presence of fine streaks of blood but in other cases the expectoration is definitely red and mucoid It is never frothy as in pulmonary edema usually it is very tenacious and adheres to the sides of the container Profuse hemoptysis occurs at times

The appearance of bloody sputum in a cardiac patient does not prove the existence of pulmonary infarction If the usual causes prevailing in noncardiac patients can be eliminated and an aortic aneurysm is ruled out pulmonary congestion may be provocative Hemoptysis from pulmonary engorgement is by no means uncommon and patients with mitral stenosis were sometimes sent by mistake to a sanatorium for the treatment of a nonexistent pulmonary tuberculosis Hemoptysis may also occur in coronary thrombosis and in paroxysmal tachycardia

Other Symptoms

Patients with pulmonary infarction may display great anxiety Not infrequently the body is bathed in a cold sweat Csell reported chills in one per cent of his cases Loss of consciousness occurs and is related to the fall of blood pressure A feeling of impending death is not rare

On rare occasions we have noted painful swallowing This pain was felt in the interscapular region and occurred when food passed through the esophageal hiatus When severe it created feeding problems Diaphragmatic pleurisy or periesophagitis has seemed to be the most likely causative factor A similar lesion may initiate persistent and exhausting hiccough

Signs

Temperature and Heart Rate The most consistent and thus the most important signs are elevation of the temperature and the heart rate Formerly both were regarded as evidence of venous thrombosis and have been called the signs of Mahler and Michaelis However it is not established that a simple thrombosis without thrombophlebitis provokes fever and tachycardia Embolisms are probably provocative

Every unexplained rise of temperature and heart rate in a cardiac patient as well as a postoperative patient should arouse the suspicion of pulmonary embolism The pulse rate may increase considerably and a tachycardia of 180 beats per minute may be reached in pulmonary embolism The fever subsides in 4 to 5 days by gradual lysis a renewed elevation of temperature suggests the development of a complication or a new embolism

Cyanosis and Jaundice Azotemia Cyanosis may be very pronounced but is often absent despite marked dyspnea Jaundice is a common finding As mentioned previously the combination of hemolysis and hepatic damage in a cardiac patient often causes jaundice The discoloration may be rather deep and may last for weeks A similar jaundice is encountered occasionally in hemorrhage with marked anemia leading to hepatic damage (ruptured ectopic pregnancy) For a long time the hemorrhagic infarct was regarded as a site for the extrahepatic formation of bile pigment

In some cases of pulmonary infarction with jaundice the nonprotein nitrogen of the blood serum reaches a level of more than 60 mg per cent coincidentally with a high value for serum bilirubin (Csell)

Examination of Lungs If the infarct is large examination of the lungs may reveal dullness of varying intensity and crepitant rales over circumscribed areas Since embolism occurs most often in the lower lobe of the right lung this area should be examined with great care On the other hand examination may fail to reveal any abnormality despite embolism and infarction often the affected area is too remote from the thoracic wall to create signs If physical signs are discovered they need not be due to infarction per se but rather to a complicating process like infarction pneumonia

A pleural effusion often forms most commonly on the right side It develops in 40 to 50 per cent of patients with pulmonary embolism In 100 cases of pleural effusion which appeared following infarction fluid developed on the right side in 51 on the left in 28 and bilaterally in 21 The fluid may possess the characteristics of an exudate and frequently is hemorrhagic Often a pleural friction rub is audible but no effusion develops Pleural irritation is common since every infarction of necessity reaches the surface of the lung

Cardiac examination reveals the tachycardia mentioned above Paroxysmal atrial fibrillation is a rare event presumably caused by acute dilatation of the right atrium with stretch of the muscular fibers (Scherf et al) Cardiac enlargement is rare unless it was present prior to the infarction or multiple infarctions (embolisms) had occured over a long period If pre existing disease has caused cardiac enlargement after an infarction dullness may rapidly develop to the right of the sternum as the result of right atrial dilatation The second pulmonic sound is often accentuated and a systolic murmur may be heard over the pulmonary artery for a few hours this bruit is sometimes called Litten s murmur although it was mentioned by Laennec Gallop rhythm is not rare

A syndrome which may lead to a remarkable dilatation of the right heart is is known as subacute cor pulmonale In patients demonstrating this syndrome because of the large heart with gallop rhythm and evidence of congestive failure the diagnosis of intrinsic heart disease is made and eventual pulmonary x ray findings are explained by the diagnosis of pneumonia This picture is seen in repeated embolization of the lungs in which therapy with anticoagulants or venous ligation often are helpful

The pericarditis occurring in a small percentage of cases apparently represents an extension from the pleurisy by continuity the mechanism is the obverse of the pleuritis which develops in the left chest after the pericarditis of myocardial infarction The pericardial friction rub may persist for a few days Occasionally pleuropericardial friction sounds are heard along the left border of the heart Disturbances of rhythm such as paroxysmal atrial fibrillation can occur as mentioned above Finally there may be a fall of blood pressure in some instances reaching shock levels

Laboratory Investigations Leukocytosis of 10 000—15 000 is found in the average case but the figures may be much higher and with an infarction pneumonia the count may reach 45 000 with predominantly polymorphonuclear cells The erythrocytic sedimentation rate rises and undergoes further acceleration if a pulmonary complication supervenes

Roentgenology may contribute to the diagnosis of pulmonary infarction The typical wedge shaped shadow with its apex directed toward the hilus and the broad base at the pleural surface is not very common More often the shadow is round because its location and projection on the chest plate determine the shape If films are taken in different positions it may be possible to discover additional infarcts The infarction shadow may persist as long as two or three months therefore particularly if there are several infarcts in the same lung the radiologic

Other Symptoms

Patients with pulmonary infarction may display great anxiety. Not infrequently the body is bathed in a cold sweat. Gsell reported chills in one per cent of his cases. Loss of consciousness occurs and is related to the fall of blood pressure. A feeling of impending death is not rare.

On rare occasions we have noted painful swallowing. This pain was felt in the interscapular region and occurred when food passed through the esophageal hiatus. When severe, it created feeding problems. Diaphragmatic pleurisy or periesophagitis has seemed to be the most likely causative factor. A similar lesion may initiate persistent and exhausting hiccough.

Signs

Temperature and Heart Rate. The most consistent and thus the most important signs are elevation of the temperature and the heart rate. Formerly both were regarded as evidence of venous thrombosis and have been called the signs of Mahler and Michaelis. However, it is not established that a simple thrombosis without thrombophlebitis provokes fever and tachycardia. Embolisms are probably provocative.

Every unexplained rise of temperature and heart rate in a cardiac patient as well as a postoperative patient should arouse the suspicion of pulmonary embolism. The pulse rate may increase considerably, and a tachycardia of 180 beats per minute may be reached in pulmonary embolism. The fever subsides in 4 to 5 days by gradual lysis; a renewed elevation of temperature suggests the development of a complication or a new embolism.

Cyanosis and Jaundice. Azotemia. Cyanosis may be very pronounced but is often absent despite marked dyspnea. Jaundice is a common finding. As mentioned previously, the combination of hemolysis and hepatic damage in a cardiac patient often causes jaundice. The discoloration may be rather deep and may last for weeks. A similar jaundice is encountered occasionally in hemorrhage with marked anemia leading to hepatic damage (ruptured ectopic pregnancy). For a long time the hemorrhagic infarct was regarded as a site for the extrahepatic formation of bile pigment.

In some cases of pulmonary infarction with jaundice, the nonprotein nitrogen of the blood serum reaches a level of more than 60 mg. per cent coincidentally with a high value for serum bilirubin (Gsell).

Examination of Lungs. If the infarct is large, examination of the lungs may reveal dullness of varying intensity and crepitant rales over circumscribed areas. Since embolism occurs most often in the lower lobe of the right lung, this area should be examined with great care. On the other hand, examination may fail to reveal any abnormality despite embolism and infarction; often the affected area is too remote from the thoracic wall to create signs. If physical signs are discovered, they need not be due to infarction per se but rather to a complicating process like infarction pneumonia.

wave in one of the leads We have seen tracings in which the QRS complexes alone underwent the modifications just mentioned whereas the RS T segments and T waves remained normal (Scherf and Boyd) The differentiation between a posterior inferior wall infarction and pulmonary embolism is not always easy in the early stage but usually it becomes possible in the following days The inversion of the T waves in the chest leads in positions 2 and 3 does not occur with inferior wall infarction causing a deep Q wave and an elevated RS T with an inverted T in lead III There are no changes in aVF characteristic for inferior infarction In cardiac infarction no S wave appears suddenly in lead I to disappear

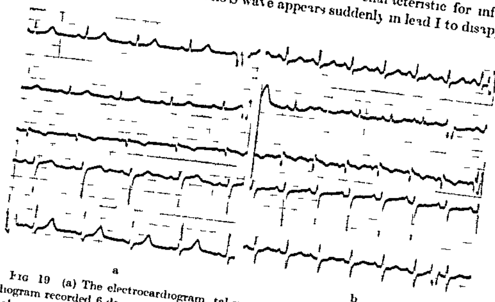


FIG 19 (a) The electrocardiogram taken preoperatively is normal (b) The electrocardiogram recorded 6 days after an appendectomy shows the typical signs of a pulmonary embolism in addition to a sinus tachycardia a deep S wave appeared in I and the Q wave is deeper in III The T wave in V 2 is slightly inverted it is lower in V 5

within a few days it is common in pulmonary embolism The electrocardiographic changes in pulmonary embolism usually persist for several days in one of our patients they remained for three weeks A small pulmonary embolus is capable of inducing electrocardiographic changes in the experimental animal The electrocardiographic changes may be found without clinical signs of pulmonary embolism and there is no parallelism between the extent of alteration in the electrocardiogram and the symptoms

Figure 19 shows a common pattern The electrocardiogram of a 48 year old man had been taken preoperatively (figure 19a) and showed essentially normal findings Six days after a successful appendectomy clinical symptoms and signs of a pulmonary embolism suddenly occurred The electrocardiogram (figure 19b) showed in addition to the increase of rate the appearance of a typical S wave in lead I which we always consider the most characteristic finding Simultaneously the Q wave in lead III became deeper The T wave in V 2 is slightly negative the

T wave in V5 is lower The other changes are readily explained by the increased rate

The changes in V2 speak against the diagnosis of an inferior wall infarction

Complications

If the patient survives the initial shock recovery usually is rapid and the danger is over in a few days However there is always the threat of a new embolism Moreover if certain complications develop the prognosis is guarded

Infarction pneumonia is a common complication In addition to the reactive inflammation surrounding the infarcted area in all patients with hemorrhagic infarction pneumonic patches appear The temperature curve undergoes a sudden rise and the systemic signs of pneumonia are present Rarely the infarcted or necrotic area becomes infected with pyogenic or putrefactive organisms so that a pulmonary abscess or gangrene occurs particularly in debilitated patients A pulmonary cavity or empyema may result from an aseptic necrosis

In cardiac patients the strain imposed on the right heart by emboli m may lead to marked hepatic enlargement and to right heart failure The latter may be resistant to therapy Not rarely new emboli appear again and again over a long period of time causing progressive right heart failure with marked cyanosis and dyspnea even in the otherwise healthy person Symmetrical peripheral gangrene has been observed although rarely (Hejtmancik and Bruce)

Differential Diagnosis

Most of the conditions with which pulmonary embolism and infarction may be confused were mentioned in the preceding paragraphs The clinical differentiation between coronary thrombosis and pulmonary embolism sometimes is extremely difficult Both conditions may be associated with severe prolonged retrosternal pain followed by a fall of blood pressure fever leukocytosis dyspnea tachycardia pulmonary signs increased sedimentation rate and electrocardiographic changes Even hemoptysis occurs in both while in some cases the existence of a lung infarct can be established Sometimes the differentiation is impossible without the electrocardiogram

The resemblance to acute abdominal conditions such as appendicitis or cholecystitis was mentioned earlier Pneumonia also causes an abdominal syndrome and the provocative mechanism is probably similar The picture of a paralytic ileus may be caused by pulmonary embolism The diagnosis of virus pneumonia or hypostatic pneumonia is often wrongly made while in other cases bronchogenic carcinoma or atelectasis is diagnosed

The responsibility of pulmonary embolism for the appearance of a bronchopneumonia may be overlooked and a distinction between infarction pneumonia and virus pneumonia may be difficult By the same token simple pleuritis may be diagnosed and the provocative infarction may remain undiscovered

Pathologic Physiology

Embolism in the main stem or in a major branch of the pulmonary artery may cause death almost instantaneously In other patients sudden severe dyspnea anxiety and pain are succeeded by unconsciousness and death in a short time Autopsy reveals a small embolism There are patients however who survive an embolism in one of the main pulmonary arteries

Reduction of the pulmonary circulation to less than 50 per cent does not necessarily produce pressure changes in the systemic or lesser circulation and ligation of a major pulmonary artery during a thoracic operation ordinarily does not have serious consequences Fatalities or very severe manifestations may occur on the other hand when a very small embolus lodges in the periphery of the lung For example Sauerbruch mentions a 32 year old patient who died suddenly after a herniotomy At post mortem nothing was found except a small embolus 3 mm in width in a minor artery within 4 cm of the lung surface In another study of 35 fatalities caused by pulmonary embolism the embolus was small in seven

These observations alone imply that the mechanical occlusion of the pulmonary vessel is not the sole reason for the serious effects of lung embolism

To explain the marked disturbances following embolism of a small pulmonary artery recourse was often made to nervous (vagal) cardiac inhibition and to shock Even vagal reflexes were incriminated However shock is often absent despite other serious symptoms and it is difficult to understand the theory of vagal inhibition since a tachycardia usually prevails moreover a direct vagal influence on the mammalian ventricle does not exist or is negligible

Recent experience indicates that certain reflex mechanisms play a major part in the development of circulatory disturbances in pulmonary embolism These reflexes may be divided into three groups (1) intrapulmonary (2) those from the pulmonary vessels to the systemic circulation and (3) pulmocardiac (pulmocoronary) reflexes

Intrapulmonary Reflexes Many experimental pathologic and clinical observations demonstrate how pulmonary embolism imposes increased strain on the right ventricle The dilatation of the right ventricle and pulmonary artery the accentuation of the second pulmonic sound and the systolic murmur over the pulmonic area speak in favor of larger demands upon the right ventricle The dilatation has been seen in experimental animals and in man The outflow tract is primarily involved as would be expected in a dilatation due to increased strain This acute rise in intrapulmonic pressure leads to the appearance of an acute cor pulmonale Massive pulmonary embolism certainly may cause such changes although extensive reduction of pulmonary circulation to 50 per cent of normal by ligation of the main right or left pulmonary artery or even obstruction of many pulmonary vessels by embolism need not create any alteration in the pulmonary arterial pressure On the other hand the intrapulmonic blood pressure may increase with a small peripheral embolism of one pulmonary artery

The part played by reflexes in causing this rise of pressure in small peripheral embolism is easily understood if we recall the situation that prevails when a peripheral artery (an artery of the leg, for example) is occluded by an embolus. In such a case rather stormy manifestations are common. The leg may be bloodless, cold, pale and immobile; tendon reflexes vanish and even sensation is severely disturbed. The situation appears to be one in which the femoral artery had been occluded. After some time, during which papaverine and other vasodilators are administered, rapid improvement may occur. Naturally, the embolus is not removed by drugs of this type; rather, there is the potential danger that because of the disappearance of vascular spasm the clot might be thrust toward the periphery where the collateral circulation is even less adequate. It seems more plausible to assume that occlusion of a small peripheral artery, as small as a muscular branch of an interosseal artery, for example, causes a reflex vasoconstriction of neighboring vessels; this spasm could produce the alarming syndrome which promptly disappears after the administration of vasodilators. The existence of a reflex vasoconstriction following irritation of peripheral arteries and veins is established, and arterial spasm in thrombophlebitis is common. Axon reflexes are responsible for this phenomenon.

Conceivably, a similar reflex spasm operates in pulmonary embolism which may elevate the pressure in the lesser circuit. The rich innervation of the lung and the existence of adrenergic pulmonary vasoconstrictor fibers make such reflexes possible.

Reflexes from the Lung to the Systemic Circulation. Increase of pressure in the lesser circuit causes a reflex bradycardia and a fall of systemic blood pressure. The reflex is released from the receptors in the pulmonary arteries and disappears if the pulmonary nerves are cut.

This reflex has been called protective since it prevents overdistension of the lesser circuit by dilating the systemic vessels. The early bradycardia observed in some patients with pulmonary embolism as well as the shocklike syndrome with marked fall of blood pressure may be caused by such a reflex mechanism (Schwiegk).

Reflexes from the Lung to the Coronary Arteries. The study of patients with pulmonary embolism who showed gallop rhythm and marked changes in the electrocardiogram but no dilatation of the right heart during life or at post mortem and no evidence of organic heart disease led to the following hypothesis (Scherf): A pulmocoronary reflex from the site of the embolus in the pulmonary artery or from the infarcted area causes the coronary arteries to narrow and leads to anginal pain, electrocardiographic changes, and even to death. There need be no actual coronary artery constriction. The signs and symptoms could be explained by the tachycardia and increased load of the right ventricle without a corresponding increase in the blood supply to the heart. This would lead to hypoxia, especially in the most sensitive areas around the papillary muscles subendocardially. The existence of reflexes from the lung and other parts of the respiratory tract to the heart is indisputable (many examples will be cited in the next chapter). The powerful influence of reflexes arising in the lung and

on the heart becomes clear to every physician who has observed patients (1) with attacks of paroxysmal atrial tachycardia which do not respond to different vagal reflexes including carotid pressure but are promptly stopped when the patient inspires deeply or (2) who developed paroxysmal atrial flutter or fibrillation whenever they took a deep breath Against the assumption that all findings *in pulmonary embolism can be explained solely by increased pressure in the lesser* circuit and in favor of the theory just advanced the following facts are cited

(1) Fatalities from pulmonary embolism occur in otherwise healthy patients who present gallop rhythm and similar symptoms without signs of increased pressure in the lesser circuit It also occurs when there is no right ventricular strain during life and no evidence for this at post mortem (figure 18)

(2) The attacks of angina pectoris in particular those attacks which respond to nitroglycerin are best explained by a myocardial ischemia

(3) In cases of pulmonary embolism the electrocardiogram shows not only the changes one would anticipate in right ventricular strain but also the alterations expected in ischemia of certain parts of the myocardium This has been re emphasized by Meyers in his recent book on the unipolar electrocardiogram The depression of the RS T in lead I the inversion of the T wave V 2 and V 3 and the elevated RS T in aVL speak for interference with the circulation in the right coronary artery

(4) The electrocardiographic changes of pulmonary embolism are not reproduced experimentally by increasing pressure in the lesser circuit e g by clamping the pulmonary artery

(5) Occasionally the changes in the electrocardiogram persist for weeks The increase of intrapulmonic arterial pressure lasts only for a few hours and the systolic murmur over the pulmonic valve area is equally transient

(6) The electrocardiographic changes often do not present a typical pattern whereas those evoked by right or left ventricular strain show constant features

(7) Acute right ventricular strain resulting from pneumothorax prolonged bronchial asthma and the like does not produce these changes in the electrocardiogram

(8) Occasionally patients have an electrocardiogram very similar to that observed in acute inferior *wall infarction Even in clinical instances* in which the right ventricle works under greater strain and there is a tachycardia and a decreased oxygen saturation of the blood the pattern of acute infarction does not appear in the electrocardiogram

(9) The presence of necroses in the myocardium especially in the wall of the right ventricle in patients dying from a small pulmonary embolism in the absence of organic coronary artery disease suggests a disturbance of the coronary circulation Moreover these necrotic areas have peculiarities of form and position which are found whenever the myocardium works under hypoxic conditions

(10) The occurrence of paralytic ileus or gastrointestinal phenomena in pulmonary embolism likewise speaks in favor of irradiating autonomic reflexes

Aviado and Schmidt reviewing reflexes from stretch receptors in heart and lungs mention unpublished experiments by Aiden that demonstrate the existence of axon reflexes in the lung One lobe of the dog s lung was supplied with blood from a donor dog Injection of glass beads into the arteries of an unperfused lobe caused reflex vasoconstriction in the perfused lobe even after the vagus nerves were cut Similarly we invoked axon reflexes for many years therefore the experimental findings of Malinow et al showing persistence of electrocardiographic changes after the vagus nerves in the neck were cut do not conflict with our explanation

Hochrein and Schneyer measured the blood flow in the coronary arteries directly and found in the right coronary artery a diminution of the blood flow following experimental pulmonary embolism Hackel et al saw a marked rise of pulmonary arterial pressure (almost three times the normal pressure) after intravenous injection of a suspension of lycopodium There were no significant changes of the coronary blood flow This alone should create myocardial hypoxia since with the greater activity of the heart an *increase* of blood flow should be needed

Comroe et al discuss the possibility that 5 OH tryptamine (serotonin) formed in blood clots by dissolved platelets (which given intravenously to cats causes not only reflex bradycardia hypotension and apnea but also pulmonary vasoconstriction and bronchospasm) is responsible for some of the signs and symptoms discussed above

Because the existence of many of the e reflexes remains undemonstrated in the experimental animal they are discarded by some physiologi ts Our inability to reproduce them however does not mean they do not exist It is not possible to reproduce many of the well recorded reflexes mentioned in the next chapter Even though it is scarcely possible to prove experimentally that gentle mechanical irritation of the rectum can cause paroxysmal ventricular tachycardia or fibrillation this undoubtedly is what happens in man under particular circumstances It will also not be easily proven experimentally that mechanical irritation of the pharynx can lead to cardiac standstill although this too probably has often occurred (but again only with a particular constellation of factors — see next chapter)

It is difficult to decide whether the reduction of coronary artery blood flow alone or the augmented strain on the right heart with unfulfilled increased requirements for oxygen is responsible The second possibility has greater appeal Experimental investigation of this problem is fraught with difficulties since these reflexes are not active in every individual (this also will be discussed in the next chapter)

Before discussing the treatment of pulmonary embolism we deem it appropriate to give a short description of the chief initiating process venous thrombosi This seems in order at least insofar as cardiac patients are concerned

VENOUS THROMBOSIS AND PULMONARY EMBOLISM

Usually pulmonary embolism is caused by thrombi from the pelvic veins or from veins in the lower extremities Intraatrial thrombi formerly regarded as very important are rarely provocative

In one of the first systematic investigations of the occurrence of venous thrombosis the condition was found in the calf veins in 27 1 per cent of 324 consecutive postmortem examinations in a general hospital (Poessle) In many cases the femoral veins were also affected In another study in which the small veins of the foot were included in the investigation venous thrombosis was found in 60 per cent of 165 non selected subjects In 52 instances the thrombosis was bilateral Thrombosis of the plantar veins usually involves the vessels of both feet and is often the primary site the thrombosis of the calf veins is often secondary This thrombosis is more common in patients with fallen arches In 100 patients with venous thrombosis of the lower extremities the calf veins were affected in 87 the plantar in 71 and the veins of the thigh in 22 (Neumann) In this series pulmonary embolism had occurred in 11 8 per cent In another investigation venous thrombosis in the leg was found in 52 7 per cent of 351 autopsies (Hunter et al) Medical cases comprised 79 7 per cent of the series If the veins of the pelvis as well as those of the extremities had been investigated the incidence of venous thrombosis would have been even greater In a statistical study of 1665 cases of postoperative pulmonary embolism that included 135 fatalities clinical as well as necropsy evidence of a venous thrombosis was missed in 24 3 per cent (Barker et al) Presumably the whole thrombus detached itself to form the embolus For unknown reasons thrombosis occurs more often in the veins of the left lower extremity than the right one

Accordingly the disease is much more common than formerly believed The clinical diagnosis is difficult and often impossible especially when the phlebothrombosis is bland and without much inflammatory reaction (thrombophlebitis)

A common condition is the one known as traumatic thrombosis that is a venous thrombosis that occurs several hours or days (up to 14 days) after blunt trauma striking the leg against a chair or stumbling against the bumper of an automobile The trauma may be so slight that patients forget it completely making the subsequent thrombosis seem spontaneous

Effort thrombosis follows an unusual effort and often occurs in the veins of the arms following backward rotation It has been described particularly in tall men after severe effort (Naide) Effort with or without rupture of muscle fibers may locally increase venous pressure so that small veins burst and a propagating thrombosis ensues

Venous thrombosis was often observed during the blitz in England when patients were seated for hours on crudely built seating devices with cross bars compressing the leg veins (shelter legs) Keeping the legs bent (a pillow under the knees) while lying quietly in bed for hours is a prolific source of thrombosis the

Gatch frame used in many hospitals to keep the knee and hip joint bent is another device that hastens thrombus formation

One may assume that during prolonged rest the weight of the leg compresses the thin walled veins and causes a lesion of the endothelium which leads to thrombosis

In cardiac patients who often suffer from congested peripheral veins and who have an abnormally nourished vascular endothelium bed rest is frequently enforced thereby often causing thrombosis in the veins of the lower extremities

An increased tendency to thrombosis has been found in patients with congestive heart failure following rapid diuresis induced by too energetic therapy It is apparently not an increased concentration and viscosity of the blood but the movement of tissue fluid into the blood stream which is responsible

Polycythemia enhances thrombus formation

Increased coagulability has also been described following the administration of large doses of digitalis and the administration of quinidine sulfate and penicillin Even fear and apprehension are said to promote coagulation of the blood The shortening of the clotting time by a fatty meal is still under investigation

While local pain fever chills redness swelling and increased temperature in the involved area characterize some cases of thrombophlebitis venous thrombosis often presents either no local signs or else merely a slight enlargement of the calf or ankle detectable only by careful measurement Pain in the plantar area is in our opinion one of the earliest signs to indicate a beginning thrombosis in the leg (Payr) The pain appears at the mesial aspect of the plantar region due to pressure of the thrombosed veins on the nerves (Denecke) Likewise of value although often absent is the appearance of soreness of the gastrocnemius region on dorsiflexion of the foot (Homan) Pain in the calf that comes with walking in low heels (slippers) is occasionally an early sign Compression of the calf by a blood pressure cuff with pressures between 60 and 150 may cause pain (Lowenberg)

The danger from noninfected latent and unrecognized thrombosis is greater than from an obvious thrombophlebitis in which the thrombus adheres firmly to the wall of the vein

Thrombosis may develop very early in postoperative and bedridden medical patients and pulmonary embolism may occur in less than 24 hours Venous thrombosis and to a greater extent lethal pulmonary embolism become increasingly dangerous in older age groups

Of great therapeutic importance is the finding that a thrombus older than 3 days is not detached Some organization of the thrombus is seen after 24 hours

Elastic stockings are applied while the patient is bedridden and always applied for 2 to 3 months or longer when the patient is ambulatory

Prevention and Treatment of Peripheral Vein Thrombosis

Therapy begins with measures to avoid peripheral vein thrombosis To accomplish this in postoperative cases walking is recommended as early as possible although some doubt exists as to the efficacy of this measure (de Bakey)

The same procedure should be followed in cardiac patients In the first edition of this book (1935) therefore it was recommended that cardiac patients with certain exceptions (such as those with coronary thrombosis) should not be kept too quiet in bed Movement of the lower extremities was suggested even for patients with acute myocardial infarction In decompensated cardiac patients enforcement of strict bed rest seems to lead almost invariably to venous thrombosis and to the danger of pulmonary embolism No harm is done in ordinary congestive heart failure if a patient is permitted to walk from one room to another to have bath room privileges or to sit in a chair Lethal pulmonary embolism has been precip itated many times simply because such patients were forced to rest Therefore in our wards absolute bed rest for this group of patients has been prohibited during the last thirty years and the results have been encouraging Recent papers by others (Dock) stress the danger of absolute bed rest and the value of this procedure It has been stated that the rarity of pulmonary embolisms in paraplegics indicates that absolute bed rest is not dangerous (Cook and Lyons) However the immo bility of such patients also prevents dislodging of thrombi

The lower end of the bed should be raised so that the legs and pelvis are elevated sufficiently to promote the return of blood to the heart The toes should be moved frequently and active or passive bending of the knees in bed should be encouraged Application of elastic bandages compresses the superficial veins and enhances the blood flow in the deep veins where thrombosis is common

Surgical intervention has found increasing popularity In recent years however the incidence of embolism in patients whose femoral veins were ligated was found to be so high and the propagation of thrombi in the pelvic veins proved so common that surgery has been almost abandoned Ligation of the inferior vena cava is rarely done since it is a more formidable procedure Further more a statistical study from the Massachusetts General Hospital showed that the incidence of pulmonary embolism did not diminish after the widespread employment of venous ligation Nevertheless we have repeatedly observed a complete change of the clinical picture after patients with subacute cor pul monale caused by repeated emboli in the lung over many weeks had a ligation of the vena cava inferior performed This operation can be life saving when anticoagulant therapy is contraindicated

Since the introduction of treatment with anticoagulants the danger of pulmonary embolism following venous thrombosis or thrombophlebitis has apparently been lessened Some claim that judicious use of these agents reduces the risk of this serious complication to less than 1 per cent Others are doubtful whether the danger of thromboembolism is markedly lessened (de Bakey) To be sure the new danger of hemorrhage is added However if all rules and contra indications are observed it is worthwhile to take the risk

Heparin Heparin is a mucopolysaccharide resembling chondroitin sulfuric acid which is found in cartilage It is said to diminish the tendency of the platelets to agglutinate and it retards the conversion of prothrombin into thrombin Its mode of action is unknown Heparin is commercially prepared from beef lung

It is found in the granules of the mast cells in the body. The chemical structure has not been precisely determined and therefore its synthesis has not been accomplished. The standardization of heparin in different countries is not the same and consequently 50 or 100 mg is not a uniform dose. One of its greatest handicaps is the fact that oral administration produces no effect.

Signs of allergy have become infrequent after foreign proteins were eliminated from commercial preparations. They do occur, however, and fever is an outstanding finding.

The effect of heparin is controlled by the estimation of coagulation time which, although it seems to be a simple determination (Lee White method or others), is actually difficult and often inaccurate; great variations are obtained if the estimation is not done very meticulously. One should try to maintain a coagulation time which is two or three times the normal value but not longer than 30 minutes.

Ulcers in the gastrointestinal tract, hemorrhagic diathesis, blood dyscrasias, excessive hypertension, old age (over 65 years), liver, renal or pancreatic damage, and subacute bacterial endocarditis are contraindications to its use. Heparin is inadvisable in thrombosis of the mesenteric vessels where the tendency to bleeding is great. Bleeding due to pulmonary infarction is not a contraindication.

Heparin should be employed as soon as the diagnosis of a venous thrombosis is made, when signs of a thrombophlebitis or of pulmonary embolism are found. The recommended doses vary. If given by intravenous infusion, 200 mg are added to 1000 ml of physiologic saline or of 5 per cent dextrose solution and the number of drops infused per minute is adjusted to the results of tests of the coagulation time. Another widely used method is to give 50 mg intravenously every 4 to 6 hours or concentrated heparin (100 mg) intramuscularly or subcutaneously twice daily. The doses are not repeated when the coagulation time is over 30 minutes. If this intermittent method is used, the coagulation time returns to normal between the peaks, that is, before the next injection is given. Clinical experience has shown that these peaks suffice to prevent thrombosis even during the hours when coagulation is normal. It seems that these peaks do not bring the danger of hemorrhage.

While Scandinavian investigators find that the estimation of coagulation time is not necessary when heparin is administered in this way, it is safer to check the coagulation time twice daily for the first few days in order to increase the dose when the patient is a hyporeactor or to decrease it when he responds too strongly.

In venous thrombosis, pulmonary embolism or thrombophlebitis this therapy is continued for 5 to 10 days, the last injections being given when the patient is ambulatory. Because of the "rebound phenomenon" it is advisable to diminish the dose gradually and not to stop the administration of the drug abruptly.

In order to prevent postoperative thrombosis and embolism, heparin is given from the second postoperative day until the patient is ambulatory.

Hemorrhages in the form of hematuria, hemarthrosis, subcutaneous or intramuscular hematoma, hemopericardium appear in about 2.2 per cent of treated cases. If evidence of hemorrhage appears and an intramuscular or intravenous injection of heparin has been given shortly before, its absorption should be slowed down with an ice bag. Blood transfusions help. The intravenous injection of 50 to 100 mg. of protamine sulfate or toluidine blue (an azo-dye) in the amount of 2 mg. per kilogram body weight serves to stop the hemorrhage quickly. Protamine counteracts heparin milligram for milligram.

Dicumarol. This substance (bis-hydroxycoumarin) was discovered in spoiled sweet clover and is the cause of certain hemorrhagic tendencies in cattle. Its cheapness represents a great advantage over heparin. Another advantage is the fact that it can be given orally. On the other hand, no satisfactory preparation for parenteral use has as yet been found. A great disadvantage is the necessity to estimate the prothrombin time daily.

Dicumarol inhibits prothrombin formation in the liver and causes a prothrombin deficiency. The prothrombin test is not simple and requires meticulous work and careful selection of the thromboplastin used. Therefore, the administration of this drug is permissible only when adequate and responsible laboratory facilities are available, and the daily dose should be given only when the result of the daily test is known. The daily amount may be given at one time and not in divided doses, since dicumarol works after a latent period of 1 to 3 days. This is, of course, a great disadvantage at the onset of treatment; it is therefore a common procedure to start with heparin and to continue with it for one or two days until the effect of the dicumarol given simultaneously becomes manifest.

Another disadvantage of the use of dicumarol is the occasional sudden and quite erratic, unpredictable change of the prothrombin time, which seems to be influenced by the intake of proteins. The values are usually said to be more stable if the patient takes 3 to 4 glasses of milk daily. Absorption of dicumarol is irregular and is increased with constipation and decreased with diarrhea. Alcohol should not be taken while dicumarol is used. No aspirin should be prescribed because salicylates have an effect similar to that of dicumarol. The hypoprothrombinemic effect of a small dose of dicumarol is much greater if congestive heart failure exists.

Contraindications to its use are similar to those of heparin, the most important being open wounds, ulcers in the gastrointestinal tract, diseases of the blood, old age, marked hypertension, hepatic disease, renal disease with disturbance of liver function, diabetes, hyperthyroidism, essential hypoprothrombinemia, poor nutrition, blood dyscrasias and subacute bacterial endocarditis. Such side effects as nausea, vomiting, or diarrhea may become so severe as to prevent their use in some patients.

The urine and stools should be watched closely and the urinary sediment examined daily for an increase in the number of red blood cells. Hemorrhage may occur in varied areas, such as the nose, rectum, kidneys, stomach, eyes and very often into the retroperitoneal tissues. This latter complication causes a rather

typical clinical picture which is often misinterpreted. The hemorrhage behind the peritoneum and the accumulation of large amounts of blood in this area may lead to sudden shock caused by the acute loss of blood or the severe pain and abnormal reflexes. If the hemorrhage takes place in the right lower abdomen, unnecessary emergency surgery may be performed for a nonexistent acute appendicitis; if located on the left side, an operation may be performed for a perforated diverticulum. Sometimes this hemorrhage leads to urinary retention. In exceptional cases who survive this event the lower abdomen and upper thigh show widespread bluish discoloration from the hemorrhagic suffusion.

Death from retroperitoneal hemorrhage seems to occur particularly in patients with peripheral arterial embolism when sympathetic block is performed while anticoagulants are being used. On the other hand, Pratt claims that this event occurs only if a large vein is torn. It must be stressed that hemorrhages do not always occur at the peak of hypoprothrombinemia. They may be missed with marked hypothrombinemia and may occur with relatively slight change from the normal level.

Serious bleeding is said to occur in 1 per cent of patients treated, milder hemorrhage in 6 per cent. Unfortunately, in our experience these accidents appear a little more frequently than the figures indicate.

The initial dose for an adult of 60 kilograms weight is 300 mg given in a single dose. It is recommended to follow on the next day with 200 mg. This is often dangerous, especially in patients with myocardial infarction and shock or in hyperreactors who are not rare. We administer the second dose after 48 hours. On the following days, when the effect of this therapy on the prothrombin time becomes manifest, the dose is adjusted to the results of the prothrombin tests. Usually 25 to 100 mg are necessary. The results of the tests are expressed in prothrombin times or in percentage of the normal. The goal is to keep the prothrombin time around double the control value of a normal individual, or between 20 and 30 per cent of normal. A normal blood sample should be tested daily in order to be sure of the activity of the thromboplastin used in the laboratory. If *the control shows prothrombin time of 14, one may say that with a prothrombin* time of the patient of 14 seconds there is 100 per cent prothrombin activity; with a prothrombin time of 22 seconds there is a 30 per cent activity; with a prothrombin time of 30 seconds, the activity is 20 per cent, and it is 10 per cent with a time of 45 seconds.

When the laboratory reports a prothrombin time of 40 seconds or more, no dicumarol is given on that day. With a prothrombin time of 35 to 40 seconds, the daily dose is 25 to 50 mg, according to whether one feels the prothrombin time to be stable or still ascending. With a prothrombin time of 30 to 35 seconds the daily dose is 50 to 100 mg, and it is 100 to 150 mg when the time is under 30 seconds.

If bleeding occurs, an intravenous infusion of 500 ml of whole fresh blood is useful, and the administration of a vitamin K_1 preparation is advised.

Vitamin K preparations are given intravenously in doses of 70 to 100 mg If the prothrombin time remains high this injection must be repeated every 4 hours Quicker and more reliable action (Gamble et al) can be obtained by the intravenous administration of an emulsion of vitamin K_1 oxide given slowly in an amount of 5 to 10 mg of phytonadione Ten to 50 mg of K_1 orally in orange juice reduce the prothrombin time within 3 to 6 hours Vitamin K_1 is now the preferred substance If the prothrombin time reaches 60 seconds 10 mg of phytonadione should be given in orange juice even without bleeding The ambulatory patient who takes dicumarol should have tablets of 10 mg of phytonadione with him take them immediately and call his physician These substances are also the treatment of choice for the anticoagulants discussed below Following the administration of large doses of vitamin K and K_1 the patient is refractory to dicumarol for from several hours to a few days

Tromexan This is a derivative of dicumarol (ethyl biscoumacetate) and represents the first new synthetic preparation of this group to promise advantages It is more rapidly absorbed and works within 24 hours Its effect disappears usually (not invariably) faster that is within 24 hours which makes it safer when hemorrhages occur It has the disadvantage however of great lability of its effect with unpredictable rises of prothrombin time Its potency is about one fifth of dicumarol and the initial dose therefore is 1500 to 1800 mg The maintenance dose is selected according to the prothrombin tests which must be done daily but it is usually 300 to 900 mg daily One tablet contains 300 mg and tromexan is given in divided doses several times a day Because of a rebound of the prothrombin level withdrawal of the compound should be gradual

Warfarin (Coumadin) sodium is a derivate of dicumarol that can be administered orally or intravenously and that produces a therapeutic level of the prothrombin time in less than 24 hours The intravenous injection acts a few hours earlier but the dosage is the same According to Clatanoff et al warfarin is comparable to tromexan in the quickness of its action The control of a stable prothrombin level seems easier

One starts with a dose of 50 to 75 mg given orally or intravenously (1 mg /Kg) The daily maintenance dose based on the prothrombin time should amount to 5 to 10 mg

Hypersensitivity is occasionally observed

In the event hemorrhage occurs vitamin K_1 is a good antidote

Marcumar (a hydroxycoumarin) is a new effective anticoagulant (Koller and Jacob Burgain et al) The dose is about 20 mg on the first day and then 3 to 5 mg daily

Phenylindanedione (phenindione) Several commercial preparations of this compound (Danilone Hedulin) are in use since Soulie employed it for the first time clinically It has dicumarol like action without being related to it Like tromexan it works quickly and is less cumulative than dicumarol The prothrombin time returns to normal within 24 to 48 hours after therapy is discontinued An average patient of 70 kilograms weight takes 150 to 200 mg as the

initial dose and 50 to 100 mg daily as the maintenance dose regulated by prothrombin tests Sometimes patients show a great resistance to this drug and do not respond with a change of the prothrombin time for days Jaundice and granulocytopenia have been reported (Shapiro) but in general this is a satisfactory preparation

Other Anticoagulants Synthetic heparin like preparations are available (heparinoids) They are effective and have the advantage of being much cheaper but they have one great disadvantage a severe alopecia may appear after these drugs are employed for a few weeks This phenomenon has been described in a mild form also after the use of tromexan and dicumarol but it is much more pronounced after the synthetic heparinoids Usually after a few months the hair begins to grow back

Therapy with anticoagulants in venous thrombosis should be continued for 6 to 10 days and then ambulation be permitted Because of the slow onset of action of many anticoagulants and the short duration of the treatment heparin is the therapy of choice

Cosgriff using anticoagulants observed 3 1 per cent embolisms in 96 patients with venous thrombosis none lethal Of 107 patients with pulmonary embolism the author found subsequent embolism in spite of the therapy with anticoagulants only in 2 8 per cent One patient died 10 minutes after the initial dose of heparin

Surgical Therapy

Venous ligation is rarely performed at present This is due in part to the fact that thrombi and pulmonary embolism originating proximal to the ligation was observed in about 6 per cent of postoperative patients Mostly however venous ligation was abandoned because therapy with anticoagulants was so successful Only in rare cases e g when anticoagulants are contraindicated or when no laboratory facilities exist is the operation performed

It should be done bilaterally the femoral vein just distal to the inflow from the vena profunda femoris being usually ligated Unfortunately a large percentage of postoperative pulmonary embolisms arise from the pelvic veins (prostatic plexuses) and ligation of the inferior vena cava although occasionally lifesaving is a formidable procedure

It is difficult to decide when a patient with thrombophlebitis or a proven venous thrombosis should be allowed to walk If bed rest is enforced for too long a period the danger of new thrombi becomes great Too early movement is associated with the danger of embolism Therefore some chance is always taken regardless of the decision

Treatment of Pulmonary Embolism

If a patient has just experienced an embolism of the main trunk of the pulmonary artery it is too late for therapy Embolectomy in pulmonary embolism is rarely applicable and success is even more uncommon

To relieve the anxiety and dyspnea in embolism of smaller arteries morphine should be given (0 01—0 02 Gm) If available an oxygen mask should be used There is some evidence that inhalation of 100 per cent oxygen widens the pulmonary arteries Since the greatest danger in embolism of the smaller pulmonary arteries is reflex vascular spasm every attempt should be made to prevent it For this purpose nitrites and papaverine in particular have been used The intravenous injection of 0 04—0 05 Gm of papaverine repeated in two hours if necessary seems to be a very useful procedure for the relief of vasospasm In addition atropine and ergotamine tartrate may be administered since clinical and experimental observations (Bardin) emphasize the importance of autonomic reflexes in the pathologic physiology of pulmonary embolism Preparations containing atropine ergotamine and phenobarbital (Bellergal tablets) are available and seem to be of help Three tablets daily may be used prophylactically in those patients who are apt to develop a pulmonary embolus We like spasmalgin a mixture of pantopon papaverine and belladonna

Phlebotomy has been recommended for relief of the markedly increased pressure in the lesser circuit Digitalis is not indicated unless the embolism occurs in a patient whose heart is already on the verge of decompensation or when recurrent emboli cause chronic strain and failure of the right ventricle In these cases unfortunately digitalis does not afford the customary rapid relief that otherwise occurs when this drug is indicated in cardiac patients

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Chapter 9

Irradiation of Autonomic Reflexes to and from the Heart

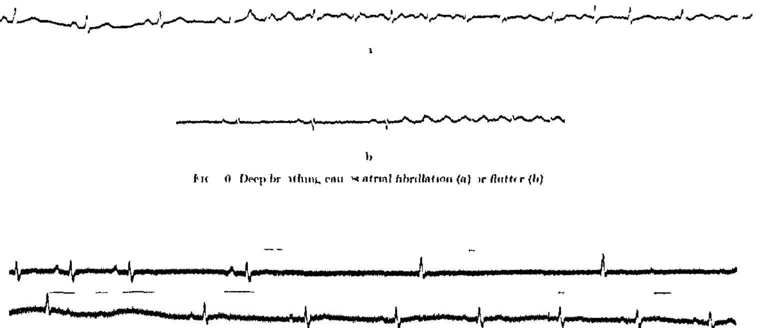
EARLIER REFERENCE WAS MADE to the great importance of reflexes in the causation of various types of dyspnea and of some disturbances following pulmonary embolism Reflexes will receive further consideration in the discussion of such subjects as peripheral vascular diseases and angina pectoris

It may not be amiss to review briefly other better known reflexes that occasionally influence cardiac action This subject has been neglected in text books and consequently though many of these reflexes are not rare their effects are unrecognized when encountered There has been some skepticism about the existence of such reflexes since often they cannot be elicited at will in man and their occurrence has scarcely been analyzed statistically Therefore the authors friends and colleagues who represent the basic sciences and who never see cardiac standstill when pleura or pericardium are opened and never see cardiac asystole when one of their animals swallows do not believe in such reflexes Nevertheless medical literature abounds with individual examples of their effect Fortunately most of this literature had been compiled at least up to 1937 in an excellent monograph (Schweitzer)

The discovery of pressoreceptors in the ascending aorta and in the carotid sinus and the recognition of their reflex influence on cardiac action blood pressure respiration the tonus of the urinary bladder stomach and intestines and on adrenal secretion and the formation of urine has led to more general appreciation of the fact that the activity of one organ may be influenced by autonomic reflexes from another distant organ (irradiation of autonomic reflexes) (Kisch)

Irradiation of sensory reflexes has been known for mo e than a century J Mueller mentioned the cold chills occasionally experienced while listening to certain classical music and the sneezing that occurs when a person leaves a dark room and is exposed to sudden light The contraction of somatic body muscles causing a chill during the contraction of the urinary bladder at the end of urination is a relatively common phenomenon in many healthy individuals and indicates an irradiation to somatic structures from an autonomically innervated organ

Disturbances of cardiac activity due to irradiation of autonomic reflexes are not rarely observed These derive largely from the fact that the activity of no other organ can be measured with the same exactitude and ease



a

b

FIG. 20. Deep breathing causes atrial fibrillation (a) or flutter (b)

FIG. 21. Voluntary respiratory standstill leads to inhibition of the sinus node with A-V nodal escape

Just as the heart may respond to autonomic reflex stimuli it may also provoke them. The diarrhea and vomiting of coronary thrombosis and the short dry cough accompanying every extrasystole in some patients exemplify reflexes from the heart to other systems (Scherf and Schott)

Reflexes from the Respiratory System to the Heart

These reflexes have been well studied and their existence is indisputable. They were examined early by experimental method.

Instillation of chloroform, ammonium chloride and other irritating substances into a rabbit's nostril causes reflex bradycardia and cardiac arrhythmia. In dogs and rabbits arrhythmias can be elicited by mechanical irritation of a certain spot on the posterior nasal septum near the middle turbinate. Not infrequently syncope is produced in man when certain areas on the nasal mucosa are touched.

Bradycardia, cardiac standstill and arrhythmias following mechanical or chemical irritation of the larynx, the trachea and bronchi have been produced experimentally in man. This may explain sudden fatalities during operations, during bronchoscopy and after the aspiration of small particles of solid food or fluid. In one patient with glossopharyngeal neuralgia cardiac arrest with syncope occurred. Section of the ninth nerve intracranially cured the patient (Ray and Stewart).

Of great interest are the cases in which deep inspiration causes atrial extrasystoles or even atrial fibrillation. One patient (Burak and Scherf) had atrial fibrillation or flutter whenever he took one or two deep breaths. During a period of observation extending over several months, attacks of atrial fibrillation could be elicited at will.

In another personal observation a 64 year old man complained of attacks of palpitation and it was discovered that transient atrial flutter and fibrillation was regularly induced by deep breathing (figure 20).

The immediate cessation of many attacks of paroxysmal tachycardia by deep inspiration or the Valsalva experiment (activation of all expiratory muscles with a closed glottis) is well known.

Of interest in this connection is figure 21, which was obtained from a 59 year old patient with coronary sclerosis, angina on effort and a sinus tachycardia. Whenever over an observation period of several weeks the patient held his breath the atrium was inhibited and deeper centers escaped. This phenomenon was observed in any phase of the respiration as long as breathing stopped. Here we are dealing in all probability not with reflexes but with an irradiation of impulse from the respiratory centers to the vagal centers.

Sudden collapse and even death during the induction of an artificial pneumothorax is often due to air embolism. When this accident happens just as the needle is inserted, reflexes may play a role and the term "pleural shock" seems justified. Mere opening of the pleura by the surgeon or ligation of a bronchus may cause cardiac asystole.

Reflexes from the Digestive System to the Heart

In 1864 Goltz reported reflex cardiac inhibition by the application of mechanical stimuli to the abdomen. shortly afterward reflex disturbances of cardiac rhythm were noted during the insertion of a gastric tube in animals.

A patient who had just been recovering from tonsillitis had ventricular standstill whenever an area in the pharynx near the soft palate was touched with a probe. The same patient developed attacks of Stokes Adams syndrome regularly on swallowing. In order to enable the patient to eat it was necessary to anesthetize the area whence the reflex was initiated (Medvei and Uiberall). A few days later the attacks disappeared completely. Attacks of paroxysmal tachycardia are often terminated when the patient puts two fingers deeply into his throat to elicit retching or an emetic reflex.

The occurrence of heart block and paroxysmal tachycardia during swallowing is not uncommon. Atrioventricular conduction disturbances have been induced by the distention of an esophageal traction diverticulum (Weiss et al.). In a patient with atrioventricular block attacks of the Morgagni Stokes Adams type appeared during straining at stool and could always be elicited by gentle digital (mechanical) stimulation of the rectum. They were due to ventricular tachycardia and ventricular fibrillation (Scott and Simcetta).

The influence of irritation of various abdominal organs (liver, gall bladder, colon) on cardiac activity — the appearance of extrasystoles in patients with gallstones, for example — is so generally appreciated that no detailed discussion is warranted. The effect of gastric or esophageal distention on coronary blood flow has been the subject of investigations, and marked changes are reported. The coronary blood flow diminishes with distention of the stomach and lower esophagus. Some patients actually complain of anginal pain when they start eating.

Other Reflexes

In lower animals (crustacea) cardiac action can easily be influenced from the skin. The arrest of paroxysmal tachycardia by mechanical irritation of the outer ear or pressure on the eyeballs is due to a reflex transmitted over the trigeminal nerve. The reduction of coronary blood flow in dogs by the blowing of cold air on the skin has considerable clinical significance.

There are other similar reflexes in which the heart does not participate. Abdominal symptoms are common in the pneumonias of children and in pulmonary embolism, as was mentioned earlier (Bingold). Paralytic ileus may occur in pulmonary embolism or extraperitoneal urologic operations (two personal observations). Ileus in nephrolithiasis, anuria from obstruction of a single ureter by a stone ("reno renal" reflex), and fainting when the rectal mucosa is stimulated by an enema illustrate the irradiation of some autonomic reflexes.

For the most part vagal fibers are used as pathways for these reflexes, but there is convincing evidence for the participation of sympathetic fibers.

Certain conditions must be present for these reflexes to appear a certain status of the receptors the reflex arc the centers and the receptive organs is necessary The importance of the status of the effector organ is shown by the fact that the same mechanism (deep breathing carotid pressure swallowing) may initiate or abolish arrhythmias

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Chapter 10

Rheumatic Fever

THE CLINICAL PICTURE OF RHEUMATIC FEVER is protean but the histologic finding are typical We are dealing with a clinical entity Despite the fact that the active disease may be unassociated with fever for a long time and may run its course without rheumatism the term rheumatic fever has been almost impervious to many attempts at replacement

INCIDENCE

Although it is a disease of major importance the exact incidence is unknown for rheumatic fever is not generally reportable in the United States and many mild cases escape recognition Possibly 500 000 to 1 000 000 people living in the United States have hearts damaged by rheumatic fever and it is estimated that rheumatic heart disease occurs in two per cent of our school children Rheumatic fever the cause of 98 per cent of heart disease in people under 20 years of age occurs most often between the ages of five and twelve It is the cause of death in almost all patients suffering from fatal heart disease between five and 24 the over all yearly death rate of this disease throughout the U S A has been between 40 000 and 60 000 The general trend both here and abroad now however seems toward a decreased incidence of the disease According to White the incidence fell from 39 5 per cent of all heart diseases in the year 1925 to 23 5 per cent in 1950 An increase in the number of instances of coronary disease and hypertensive heart disease may make this decrease more apparent than real

ETIOLOGY

Relationship to Group A Hemolytic Streptococci Although the cause of the disease is unknown some relation between rheumatic fever and infection with group A hemolytic streptococci (of which more than 40 subtypes exist) seems established Repeated infections appear necessary It is estimated that rheumatic fever follows three to five per cent of all streptococcus infections including scarlet fever The disease seems to be caused by sensitivity to antigens against protein products of certain forms of streptococci Viral infections have been repeatedly suspected but without proof Epidemics of streptococcic pharyngitis or tonsillitis have been followed in seven to 21 days by epidemics of rheumatic fever Such incidents have been observed in barracks training centers schools and camps The streptococcus infection is often subclinical An infection of the

upper respiratory tract a few days to a month prior to rheumatic fever is a common occurrence in a large number of cases Rheumatic fever may also follow an infection elsewhere e g after an appendicitis

The apparent success with which antibiotics given early during a streptococcal infection prevent the appearance of rheumatic fever and the effect of sulfonamide and penicillin prophylaxis in preventing recurrences speak strongly in favor of streptococcal infection as an etiologic factor

The increased titer of antistreptococcic lysins and other serologic reactions obtained in the blood of patients with rheumatic fever is also suggestive of the etiologic role of streptococcic infection but it is still not conclusive evidence

Overexertion chilling trauma (Glazebrook and Thomson) and vaccination against smallpox (Freud) may lead to a recrudescence or recurrence of an attack These factors are more comprehensible in view of the work of Selye who demonstrated that arthritis and myocardial lesions similar to those seen in rheumatic fever are found as a consequence of stress and belong to the picture of the general adaptation syndrome

Allergy At present it is widely assumed but not proven that rheumatic fever results from a chronic streptococcal infection which in some individuals causes the connective tissue to respond abnormally with exudation and proliferation Myocardial and coronary lesions similar or according to some identical to those of rheumatic fever can be obtained by injecting horse serum into rabbits to produce anaphylaxis or serum sickness This supports the opinion of those who regard rheumatic fever as the consequence of a hypersensitivity to bacterial products

Accordingly the pathogenesis of rheumatic fever is explained by the existence of hypersensitivity to streptococci resulting from repeated low grade infections or the persistence of foci of infection in the body Under suitable conditions when certain organisms or their products are disseminated in the tissues these tissues react abnormally producing the characteristic picture of rheumatic fever While this hypothesis as well as variants designed to embrace the hereditary and environmental conditions are not uniformly accepted allergy or some related state appears to be the most acceptable theory for the pathogenesis of rheumatic fever pending further discoveries

Heredity This seems to play a role for genetically susceptible individuals acquire the disease at an early age The appearance of several instances of rheumatic fever in a single family however has been explained by an exposure to the same infection the same nutrition and the same living conditions — in other words to environmental conditions

Social Status Rheumatic fever was once called a disease of the poor for it was believed to be associated with living in dampness overcrowding and poverty While it is more frequent in the slums it is by no means rare in higher income classes

Race Racial susceptibility has not been established

Age Rheumatic fever is primarily a disease of infancy and childhood Acute rheumatic fever has been reported in the newborn (Kissane and Koons) but in these cases the mother invariably seems to have suffered from the active disease during pregnancy Although it is not rare in children at the age of two years the peak of incidence is between five and twelve When the age of 15 years is reached *70 per cent of the patients have already been affected* The acute manifestations become rare in older individuals but instances of the first attack after the age of 60 years are known An apparently first attack of acute rheumatic fever has been observed in a patient 74 years of age During the past year we have observed three instances in a hospital caring for 2000 aged patients all three cases were beyond the age of 65 but we were unable to determine whether this attack was the first

Sex There is no striking difference in incidence between the two sexes in most regions but girls seem particularly susceptible in some areas The disease tends to appear somewhat later in boys than in girls

Avitaminosis In respect to nutrition a deficiency of vitamins (A B C and even D) has been frequently asserted to favor the development of the disease Crucial evidence that vitamin deficiency has etiologic importance in rheumatic fever has not been provided The low blood levels of vitamin C frequently reported may be due to an inability to utilize the vitamin during the disease

Proteins in Diet Of interest is the statement that rheumatic fever is less common in farming areas than in places where the diet is deficient in proteins eggs in particular

Climate The role of climate in the incidence of the disease is not definitely established Rheumatic fever is more common in cold than in warm climates and is more frequently encountered in the changeable weather of the northeastern Atlantic states and of the British Isles than in Arizona Florida or California However it is frequent in dry and sunny Colorado In the New England states and the eastern section of the United States the disease is more prevalent in late winter and early spring than in summer or early autumn (Sutton) In the tropics the disease is rare except on high plateaus (Clarke) Its occurrence becomes less frequent if endangered patients are removed to subtropic climates where streptococcal infections are less common This prevails only while the patient remains there for return to cold climate often leads to reactivation

PATHOLOGY

The first change seems to appear in the mucoprotein ground substance of the collagenous tissues (Klinge) It is associated with swelling and necrosis of the latter

The *Aschoff body* is essential to the histologic diagnosis of rheumatic fever It has never been found in man in other conditions This pathognomonic lesion when fresh *consists of a small focus of necrosis scattered lymphocytes and* peculiar large epithelioid cells arranged in the shape of a fan This granuloma is specific for rheumatic fever although the large cells with their peculiar nucleus

alone are not characteristic In the myocardium the Aschoff body ultimately disappears leaving a scar

The interfibrillary ground substance consists of chondroitin sulfuric acid and hyaluronic acid The latter is depolymerized by an enzyme hyaluronidase The relation of this enzyme to rheumatic fever has been widely discussed of late but is not clear A certain spreading factor which increases tissue permeability has been discovered in testicular extracts and group A hemolytic streptococci This factor was recognized as hyaluronidase and this substance is antigenic The amount of antihyaluronidase is greater in patients with rheumatic fever Salicylates are reported to inhibit the spreading reaction of hyaluronidase and the antirheumatic effects of this drug have been attributed to this action Crucial evidence has not yet been submitted

Rheumatic fever is a disease of the mesenchyme and involves connective tissue everywhere However the responses in different organs vary Thus typical Aschoff bodies are not found in the lungs although perivascular infiltrations and alveolar exudation appear they are also absent from the brain

Vascular System Inflammatory reactions are often discovered at the root of the pulmonary artery and aorta Similar changes occur regularly in the systemic arteries in the peripheral vessels of the lungs and especially in the coronary arteries They consist of round cell infiltrations changes in the intima media and adventitia with hyaline exudate which obstructs the small vessels A glomerulitis is demonstrable in over 20 per cent of the cases

Joints and Serous Surfaces The same changes are noted in the joints and in some serous surfaces such as the pleura and pericardium In these tissues the exudate is predominately serous The joint cavity may be distended by fluid exudate which contains fibrin and a few granulocytes The synovia is edematous and hyperemic The periarticular tissues are involved in a similar manner and Aschoff bodies may persist in these structures for a long time

Heart In the heart myocardial involvement with the formation of Aschoff bodies seems to occur in 100 per cent of the cases (Talalaeff) This holds at least for all cases of fatal rheumatic fever Myocardial changes are also caused by the vascular alterations mentioned above by degeneration of the myocardial fibers diffuse myocarditis and infiltration with eosinophilic leukocytes

In a large percentage of cases changes appear in the endocardium along the line of closure of the valves This happens particularly on the atrial surface of the mitral and tricuspid valves and on the ventricular surface of the aortic valves Here also swelling of the fibers and of the ground substance secondary necrosis of the fibrils and migration of granulocytes and fibroblasts are the primary changes Secondary deposits composed principally of fibrin produce small warty vegetations verrucous endocarditis At the beginning the verrucae can easily be removed but invading capillaries and fortifying connective tissue gradually attach them more securely to the valve Verrucae also appear on the chordae tendineae and on the endothelium of the chambers The mural endocardium of the posterior wall of the left atrium is often affected Healing leads to

thickening of the endocardium and valves to retraction stiffening and fusion of the cusps and valves and to shrinkage and fusion of the chordae tendineae with eventual secondary degeneration and calcification Frequently the pericardium is also involved (pancarditis) Involvement of the valve rings and ascending aorta as well as pulmonary artery occurs and facilitates later enlargement of these structures if failure and congestion develop

The pericardial changes are described in a later chapter Marked alterations are also found in the diaphragm

Lungs Apart from ordinary bronchopneumonia other pulmonary complications may appear which are characterized clinically by fever severe cough and bloody sputum dyspnea occurs in these patients In this rheumatic pneumonia an alveolitis is found with buds of connective tissue filling and obstructing the alveolar ducts They have been called bourgeons conjonctifs or Masson bodies and they are said to represent the characteristic pulmonary equivalent of the Aschoff body in rheumatic fever The specificity of the Masson bodies has been recently denied (Herbert and Manges) Atelectasis is common Physical findings may be scarce X ray studies show massive density or radiation of opaque shadows from the hilus into the lung fields The arteries of the lung especially in the smaller divisions may show an obstructive arteriolitis Acute fibrinous or serofibrinous pleurisy also occurs with or without pneumonitis

Subcutaneous Tissue The firm rounded subcutaneous nodules are gray and translucent They are composed principally of edematous connective tissue and cellular infiltrations lacking definite arrangement The presence of Aschoff bodies in these nodules is exceedingly rare

Nervous System Proliferative arteriolitis with occlusion of small vessels and focal malacia of the central nervous system especially of the cortical gray matter and meninges have been described repeatedly The pathologic picture often resembles a meningo encephalitis but the spinal fluid usually remains normal These changes are mentioned to explain the acute and even chronic psychoses such as schizophrenia which may follow rheumatic fever Epileptiform convulsions are said to be seven times as common in patients who have had rheumatic fever as in the general population (Foster)

Atherosclerosis Atherosclerosis especially coronary sclerosis is often considered a final stage of the arterial involvement in rheumatic fever It seems however that rheumatic fever does not predispose to coronary sclerosis Experience shows that the incidence of coronary atherosclerosis is no higher in rheumatic fever patients than in nonrheumatics despite the fact that the coronary artery lesions described above are demonstrable in approximately one half the patients dying of an acute attack of rheumatic fever

SYMPTOMS

Insidious Onset Often the onset is very insidious so that the disease is easily overlooked Accordingly the number of patients is rather large (30 to 40 per cent) who at a later date develop complaints from a valvular lesion due to an earlier

but entirely unrecognized rheumatic fever This feature and the fact that cardiac changes are not invariably permanent make the compilation of accurate statistics exceedingly difficult

General Symptoms In many cases loss of appetite profuse sweating loss of weight irritability fatigue restlessness slow growth abdominal pain and lassitude as well as anemia are the first and sometimes the only manifestations of the disease Epistaxis is common Since salicylates have an anticoagulant action some authors attribute the epistaxis to the administration of large doses of salicylates Epistaxis often occurs however in acute rheumatic fever before any medication has been given

So called growing pains are common manifestations of a synovitis localized in the region on the hamstring tendons behind the knee but they may have other causes which are not related to rheumatic fever In the latter instance they are usually felt in the muscles and tendons rather than in the joints They are rare in the upper extremities and do not cause pain on motion

Local Symptoms The clinical picture of an acute migratory arthritis with inflammation redness extreme tenderness and swelling of the joints successive involvement of one joint after another and the tendency to involve the large (knee elbow) as well as the small joints (bones of the hands feet spine jaw) is well known This syndrome of acute polyarthritis is more common in childhood and becomes infrequent with increasing age The arthritis may be monoarticular and need not migrate Return of normal joint function within a short time is the rule

At other times the disease may begin abruptly with vomiting acute abdominal pain and tenderness in the right lower quadrant This may suggest acute appendicitis (pseudosurgical cases) The abdominal pain has been explained by the presence of an arteritis in abdominal organs as well as by a rheumatic mesenteric lymphadenitis These abdominal signs respond well to salicylates Cardiac symptoms symptoms indicating pulmonary pathology or involvement of the nervous system may dominate the clinical picture

Pain over the precordium or retrosternal pain is very common and in most cases is due to involvement of the coronary vessels it may become aggravated if acute pericarditis develops

The widespread involvement of small arteries in active rheumatic fever accounts for the protean picture

SIGNS

Fever Fever is often absent If present it may persist for days or months While it may develop into a hyperpyrexia of 111 degrees F this is rare Temperatures of 103 degrees F are common There is profuse sweating

Joints An important sign suggestive of the correct diagnosis is redness and swelling of the joints with periarticular inflammation causing pain which is sometimes extremely severe This statement is particularly valid when the original joint involvement subsides in approximately eight days while other

joints are successively invaded in the interim In classical cases the arthritis is associated with general malaise pallor anorexia and weight loss Cold clammy sweats and profound prostration are also present In these cases the diagnosis is simple In the absence of joint involvement however diagnosis by physical examination alone may be exceedingly difficult

Skin Erythema multiforme is common Erythema marginatum (circinatum annulare) with pale centered ringlets over the flexor surface of the joint is considered pathognomonic Erythema nodosum and purpuric eruptions also occur as unspecific reactions

Subcutaneous Tissue The occurrence of subcutaneous rheumatic nodules is considered frequent in some countries and relatively uncommon in others Such nodules are infrequent in adults They are reported in approximately 1 to 4 per cent of the American cases but the latter figure presumably includes more juvenile cases Since the nodules are painless the search for them must be conducted with patience in the areas usually affected the extensor surface in the neighborhood of the elbows wrists and knees and over flat bones as in the scalp They are often symmetrical They appear in crops and may persist for weeks When large they are readily detected but small ones require careful palpation because the non tender masses may be no larger than peas Later the nodules become firmer fibrous and more circumscribed These rheumatic manifestations which disappear as healing occurs are important because they constitute a sign of activity Some consider them a sign of a more virulent process

Lungs Pneumonitis is not uncommon Some authors found it in 11 per cent of the cases It begins with fever dyspnea cough and pleural pain and imitates the picture of atypical pneumonia It seems particularly common in children and may lead to a fulminating clinical picture and death Rales and dullness are found Roentgenograms show bilateral symmetrical multilobular infiltrations often simulating pulmonary edema (Seldin et al) Pleurisy with effusion is common

Heart Since cardiac involvement is exceedingly common and acute myocarditis seems to be invariably present during the active phase examination of the heart may aid in the diagnosis Moreover repeated careful observation of the heart is necessary especially in early childhood for many of these patients succumb to cardiac complications during the active phase

A sinus tachycardia is present and the heart rate may reach 140 per minute The cardiac rhythm is usually regular since the respiratory arrhythmia otherwise so common in the healthy heart particularly during childhood tends to disappear In some cases arrhythmias due to conduction disturbances (periodic dropped beats or Wenckebach s periods) develop Extrasystoles and atrial fibrillation are rare

Palpation reveals a hyperactive heart as in hyperthyroidism This hypermotility is also demonstrable fluoroscopically and in the absence of other diseases (hyperthyroidism anemia cardiac neurosis) is considered a valuable sign of active rheumatic carditis The heart may be enlarged This always indicates severe

myocardial damage an ominous development if it occurs early in the active phase Cardiac dilatation is frequently seen in ambulatory patients in whom marked myocardial damage existed and in whom the diagnosis was overlooked for some time Occasionally this dilatation disappears rather quickly as the patient recovers from the acute phase In many cases the enlargement of the cardiac shadow is more apparent than real since it is due to the formation of a pericardial effusion

At times the heart sounds are impure distant and split Since splitting or duplication of the heart sounds is a common event in normal people particularly in childhood this does not necessarily mean cardiac involvement but sudden appearance of this sign is important A presystolic gallop occurs if conduction time is prolonged With more severe myocardial damage the sounds are muffled and a diastolic type of gallop rhythm is heard The differentiation of this type of gallop rhythm from the physiologic third heart sound which is common in children may be impossible (see chapter on myocardial diseases)

Systolic murmurs over the apex and the pulmonic area are heard frequently Changes in the valvular ring with consequent relative mitral insufficiency and edema of the valves are offered as an explanation of the former while a rheumatic mesopulmonitis with dilatation of the supravalvular portion of the pulmonary artery and formation of eddies is held responsible for the latter Probably the cardiac hypermotility tachycardia and the fever contribute to the appearance of systolic murmurs These early systolic murmurs do not indicate valvular involvement for it requires many months before the connective tissue can shrink sufficiently to produce actual valvular changes

In 75 per cent of the cases these systolic murmurs disappear within six months In many patients with acute rheumatic fever no lasting disturbance of cardiac function remains The longer and more severe an attack the more probable is involvement of the valves At the termination of the first attack of rheumatic fever Ash found no evidence of heart disease in 59 2 per cent of the patients

Diastolic murmurs have been described repeatedly in the acute phase They are transient and are explained perhaps by the rapid diastolic influx of blood into the dilated ventricles Often impure sounds and diastolic accidental sounds are confused with murmurs indicative of structural damage A pericardial friction rub is audible in a large percentage of the childhood cases when the search is repeated sufficiently often and with great diligence Effusions are common

Laboratory Tests The white blood cell count the sedimentation rate the electrocardiogram and other tests are important and may help establish the diagnosis and aid in estimating the progress and in detecting recurrences The findings are not characteristic of rheumatic fever but they yield invaluable information in conjunction with other clinical data

Leukocytosis is common the total figure may exceed 20 000 A count above 9000 is considered by some indicative of an active process With relapse the white blood cell count rises sometimes before other evidence of the recurrence is demonstrable Persistent leukocytosis often but not invariably speaks in favor of con

tinued activity A normal leukocyte count however does not preclude an active process

Usually a progressive anemia due to bone marrow depression develops rapidly early in the active phase

Urine Marked sweating occasionally results in a drastic reduction of the urinary output The specific gravity of the urine rises and the color is dark Often the highly acid urine deposits urates on cooling Albuminuria is not uncommon in the febrile cases and red blood cells may be found in the sediment The latter findings are important and should be checked frequently sometimes hematuria has been reported to be the result of salicylate therapy Acute nephritis occurs but its relationship to rheumatic fever is not clear

Erythrocytic Sedimentation Rate This test or Weltman s coagulation test has primary importance in determining the degree of activity of the process Figures of 100 to 130 (Westergren method) are not rare in the active stages of the disease Sometimes tachycardia and increased sedimentation rate are the sole indications of persistent activity at other times only the latter is found But exceptions that is activity in spite of a normal sedimentation rate are not rare This became clear when the appendices of the left atrium were resected during commissurotomy in patients with mitral stenosis Histologic examination revealed Aschoff bodies in 30 per cent of the specimens examined despite absence of clinical evidence of activity According to some authors these Aschoff bodies represent a healed stage (Tedeschi et al) When pulmonary congestion supervenes the rate of red blood cell sedimentation is lowered

Streptococcal hemolysins dissolve red blood cells Antibodies are formed which are called antistreptolysins Individuals who have recently had a streptococcal infection form an antibody which neutralizes the O (oxygen labile) hemolysin of certain beta hemolytic streptococci The titers in rheumatic fever are high in 85 per cent of the cases in the active phase But similar titers (250 and above) *are seen for a long time following any streptococcal infection The test is not* specific and does not indicate progress of the lesion

C reactive protein Apparently this is one of the most valuable tests During various infections *or necrotizing processes a protein appears in the* blood which reacts differently from any other blood protein with the C polysaccharide of pneumococci in vitro It is a precipitation reaction This antibody is developed by hemolytic streptococci A precipitate is formed with a test reagent consisting of antiserum prepared in rabbits by immunization with purified C reactive protein However the test may be negative despite activity of the process On the other hand it is not reversed by congestive heart failure as is the sedimentation rate It is suppressed by salicylates cortisone and ACTH and is absent in normal blood There is thus no normal range Any positive reaction is abnormal

MUCOPROTEINS Estimation of the concentration of mucoproteins in the serum has been said to be a useful index of rheumatic activity The test is nonspecific The mean value for healthy children is 2 5 mg percent In rheumatic children values of 8 5 mg per cent are found

OXALACETIC TRANSAMINASE In active rheumatic fever the serum concentration of the enzyme glutamic oxalacetic transaminase is increased (Nydick et al)

Electrocardiogram This is altered in most instances of active rheumatic fever if tracings are registered sufficiently often changes are found in 95 per cent of the cases The changes may come and go within a few hours — ten negative tracings may be followed by a positive one Frequent registration of the electrocardiogram in active rheumatic fever has served to reveal the high incidence of myocardial involvement and the peculiar affinity of this disease for the specific tissue of the heart Prolongation of the P R interval is the most common finding The normal P R interval should not exceed 0 16 second in infants 0 18 second in childhood and 0 21 second in the adult In rheumatic fever the values often exceed 0 21 second Occasionally higher degrees of block or even complete heart block appear These changes are usually transitory Some maintain that prolonged atrioventricular conduction time is due to increased vagal tonus or to an increased response of the heart muscle to vagal stimuli since the prolongation is abolished by atropine This conclusion seems unwarranted in view of the fact that the normal conduction time is also markedly shortened by this drug In rare cases the P P interval remains permanently prolonged after full recovery of the patient

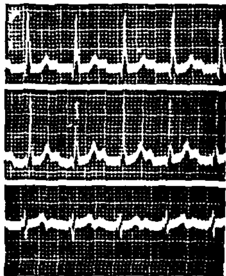


FIG 22 Sinus tachycardia and prolonged atrioventricular conduction time (0 26 second) in a patient with active rheumatic fever

Figure 22 shows an electrocardiogram obtained from a 12 year old boy with active rheumatic fever The atrioventricular conduction time is prolonged to about 0 24 second There is a tachycardia of 124 beats per minute since P is *hidden in the T the exact measurement of the beginning of the P wave is impossible Abnormal T waves and evidence of intraventricular block especially right* bundle branch block often occur

CLINICAL COURSE

The manifestations and duration of the active phase of rheumatic fever varies In the past overemphasis has been laid on the joint manifestations often they are absent Mono and polycyclic forms have been described the first being about twice as common as the second In the monocyclic type only *one series* of joints is affected in rapid succession whereas in the polycyclic type there are repeated exacerbations with and without joint manifestations over a long

period of time There is also a continuous form which persists for several years

The elevated sedimentation rate increased leukocyte count and other evidence show that the period of activity frequently lasts for years although much of its evolution is subclinical At other times notably in early childhood the stormy signs of activity may be fulminating and the manifestations are alarming Within a few weeks either the severe myocardial damage causes congestive heart failure which does not respond to treatment or else a pericarditis develops In many of these cases death cannot be prevented Sometimes the initial picture is rather severe but the subsequent recovery proceeds without leaving much trace of damage as far as the clinical examination reveals

In general the course of rheumatic fever is unpredictable and variable but the cases can be grouped readily into three categories

(1) Cases in which the process dies out entirely leaving the patient without cardiac damage or with a minimal injury compatible with a long and active life

(2) Cases in which the patients develop a valvular lesion following the first or second attack of rheumatic fever which persists compensated for a variable time often throughout a long and active life

(3) Cases in which the process is active for many years with frequent relapses increasing disability and death at an early age

All possible variants of these three groups may be found

Fortunately hyperpyretic rheumatic fever is rare In this variety temperatures of 43 degrees C and higher occur and the cerebral centers regulating temperature are presumed to be affected perhaps as a part of an encephalitis These patients usually have delirium a symptom otherwise uncommon as long as rheumatic fever is uncomplicated and the patient has not received large doses of salicylates Skin eruptions are frequently present most of the patients succumb

Recurrences of rheumatic fever are common especially in children but are less frequent after the age of 14 years Many patients in the childhood group who recover from rheumatic fever suffer from a recurrence within one year The average risk for a major recurrence of rheumatic fever is 25 per cent in patients who are four to 13 years old and 8 6 per cent in patients between 14 and 16 The risk of a major recurrence is many times greater in the year following a period of active rheumatic fever than in subsequent years (Wilson and Lubschez) It is often difficult to decide whether we are dealing with a recurrence or a recrudescence of an existing attack These observations have an important bearing on prophylactic measures especially in endangered children

For reasons already mentioned and particularly because so many cases of rheumatic fever escape diagnosis it is difficult to ascertain the incidence of permanent cardiac disease If obervations are limited to people known to have had active rheumatic fever residual cardiac disease may be expected in 85 per cent Others as mentioned above place the incidence at 50 per cent or less but all agree that the percentage rises with subsequent attacks Another factor in statistical variation is the duration of the follow up often the time elapsing after the acute phase is too short for a positive statement In a four to eight year

follow up study of veterans Engleman Hollister and Kolb found rheumatic heart disease as a sequel to rheumatic fever in 23 7 per cent of 135 men In a study of 1000 patients with rheumatic fever Bland and Duckett Jones found evidence of rheumatic heart disease in 44 per cent at the end of an observation period of 20 years

Signs of Activity These are fever joint inflammation increased sedimentation rate positive C reactive protein leukocytosis temporary changes in the electrocardiogram tachycardia and the presence of subcutaneous nodules Only one or two of these signs need be present

DIFFERENTIAL DIAGNOSIS

Occasionally this is very difficult Earlier when discussing the gastrointestinal symptoms of rheumatic fever we alluded to a possible confusion with appendicitis

The differentiation between rheumatic pneumonia and pulmonary congestion is likewise often difficult while stiffness of the neck or delirium may simulate meningitis The pulmonary manifestations may lead to the diagnosis of bronchopneumonia or pleurisy and the renal changes with subsequent hematuria and cylindruria may suggest the erroneous diagnosis of acute nephritis Confusion with poliomyelitis is said to be common

Great care must be exercised to exclude an arthritis of gonococcic origin Not rarely the latter may be polyarticular whereas rheumatic arthritis may be limited to a single joint so that the opportunity for error is great The rapid relief afforded by adequate doses of salicylates in rheumatic fever may help in the differential diagnosis of this type of arthritis

Very difficult is the differentiation between rheumatic fever and the syndrome following infection with streptococci Joint pains and cardiac changes appear in both conditions This question is discussed in the chapter on myocarditis The wrong diagnosis of influenza is often based on noncharacteristic complaints and fever

There are several acute infectious diseases which may be associated with a secondary polyarthritis The related features of scarlet fever dysentery and so forth usually make the differential diagnosis relatively easy Likewise the circumstances under which a septic arthritis with great joint destruction develops usually precludes diagnostic errors Unfortunately this is not always the case in an acute osteomyelitis Osteomyelitis has a more intense local symptomatology and the process is at the epiphysis rather than in the joint moreover the constitutional reaction is severe Nevertheless childhood osteomyelitis is often considered rheumatic fever until sepsis develops the mistake may be fatal Rheumatic fever may also be confused with undulant fever and miliary tuberculosis (Freud et al)

According to the modified criteria of Jones for the diagnosis of rheumatic fever the presence of two major criteria or one major and two minor criteria indicate a high probability of the presence of rheumatic fever

Major criteria are (1) carditis (as manifested by the presence of significant murmurs increasing cardiac enlargement as seen by x ray examination pericarditis congestive heart failure in the absence of other causes) (2) polyarthritis (3) chorea (4) subcutaneous nodules and finally (5) erythema marginatum

Minor diagnostic criteria are fever arthralgia prolonged P R interval in the electrocardiogram increased sedimentation rate presence of C reactive protein and leukocytosis and evidence of preceding infection with beta hemolytic streptococci The presence of a previous history of rheumatic fever or of inactive rheumatic heart disease are also minor diagnostic criteria

Sickling Disease In sickling disease the appearance of dyspnea arthritis cardiac enlargement with a prominent conus of the pulmonary artery the presence of systolic and even diastolic murmurs and changes in the electrocardiogram may cause confusion Anemia and thrombotic occlusion of small pulmonary and coronary arteries seem responsible for many of these findings The presence of lymphadenopathy jaundice anemia reticulocytosis no response to salicylates and a normal sedimentation rate speak in favor of sickling disease The possibility that in rare instances rheumatic fever and sickling disease may coexist (Plachta and Speer) should be borne in mind

Rheumatoid Arthritis In adults active rheumatic fever often resembles rheumatoid arthritis since the latter disorder may start in abruptly with all features of rheumatic fever Subcutaneous nodules occur in 15 to 20 per cent Sometimes distinction is possible only after prolonged observation since the initial picture is the same as in rheumatic fever Formerly narrowing of the joint spaces and limitation of motion as well as poor response to salicylates were considered suggestive of rheumatoid arthritis In recent years cardiac manifestations such as electrocardiographic changes the appearance of valvular lesions and the like have been reported in rheumatoid arthritis Among 25 cases of infectious arthritis 14 showed evidence of cardiac involvement identical with that found in rheumatic heart lesions (Baggenstoss and Rosenberg) Even structures resembling Aschoff bodies and subcutaneous nodules have been reported There is much support for the opinion that both conditions are variants of the same pathologic process (Klinge) The occurrence of cardiac manifestations in such patients however is more rare in our experience than is indicated by some authors On the basis of their experience with 100 patients with rheumatoid arthritis and 13 postmortem examinations Egelins et al denied that the incidence of myocarditis or endocarditis is increased

PROGNOSIS

Many patients succumb in or shortly after the active phase of this highly serious disease while a large number die in the prime of life from its consequences

Generally speaking the prognosis is more serious when the initial manifestations are severe when activity persists for a long time or when the disease begins early in life Only 69 per cent survive childhood and only 35 per cent live through adolescence when the process starts early Fifty per cent of the patients

die within nine years of the onset and only five per cent live beyond the age of 45 (Cohn and Lingg) The more pronounced the myocardial damage is and the earlier cardiac failure develops the worse the prognosis If a permanent valvular lesion develops the prognosis depends mainly upon such recurrences and complications as atrial fibrillation or pulmonary embolism Nevertheless it is not uncommon to see a patient who developed a rheumatic valvular lesion at the age of five or six years and is still active and well at 70 or 75

A good deal depends upon the treatment during the attack and thereafter In this respect the great advance made in recent years justifies the hope for remarkable improvement in the prognosis in the near future

CHOREA

Sydenham s chorea is related to rheumatic fever but the precise association is obscure It is a childhood and adolescent disease and is more common in girls whereas as mentioned earlier rheumatic fever affects both sexes equally Sulkiness and emotional outbursts are early signs

Many physicians regard chorea simply as another manifestation of rheumatic fever In 20 per cent of cases of chorea rheumatic heart disease develops although there has been no other evidence of rheumatism (Sutton and Dodge) According to other studies the incidence of heart disease in cases of pure Sydenham chorea is over 50 per cent Some observers believe chorea is succeeded by cardiac complications only when there has been other evidence of rheumatic infection It is even asserted (Usher) that valvular disease is never the consequence of chorea per se but rather that it is due to an intercurrent rheumatic infection In one patient with signs of chorea but no other evidence of active rheumatic fever however death occurred accidentally and an active rheumatic endocarditis was found at necropsy (Sutton and Dodge)

While leukocytosis and fever may be absent in chorea it is possible that these signs of activity have vanished by the time chorea appears The sedimentation rate in chorea is normal

Of 134 patients with chorea without any other manifestation of rheumatic fever only 3 per cent developed heart disease (Jones and Bland) The authors consider chorea to be a mild manifestation of rheumatic fever not particularly conducive to the development of rheumatic heart disease

Pheumatic endarteritis of the cerebral vessels (meningoencephalitis) with perivascular infiltrations has been observed and pronounced changes may be found in the corpus striatum

TREATMENT OF PHEUMATIC FEVER

A distinction should be made between the treatment of the active phase of rheumatic fever and the measures designed to prevent a recurrence

Bed Rest This is necessary in active rheumatic fever and must be *enforced* as long as signs of activity persist and at least three weeks after the sedimentation

rate returns to normal Increased heart rate fever and progressive electrocardiographic changes are also indications for rest Bed rest need not be absolute in a majority of cases — the patient may have bathroom privileges

Prolonged rest is extremely important for despite the acuteness of some of its manifestations rheumatic fever is a chronic disease The process may be active and progressive even in the absence of symptoms of poor health

In the acute stage with arthritis some thought should be given to the proper type of bed as well as to suitable clothing in view of the severe sweating attention to these details will add greatly to the patient's comfort The situation is much the same as in tuberculosis a disease comparable to rheumatic fever in many respects Since it is impossible to predict the duration of activity of the disease rest should be enforced for three weeks after all evidence of activity has vanished

Drugs The therapeutic agent of choice for the management of acute rheumatic arthritis is sodium salicylate which has been employed for more than half a century in this disease Many observers believe that the drug furnishes such prompt relief that this in itself may provide a therapeutic diagnosis While there are patients who do not respond those whose joint pains are not caused by rheumatic fever may obtain relief from salicylates It seems that sodium salicylate does not influence the course or duration of the disease nor the progress of complications but it is capable of rapidly dissipating the joint swelling relieving pain and acting as an antipyretic Large doses of sodium salicylate at regular intervals are recommended A typical daily dose might be one grain per Kg body weight or 10 grains every 4 hours It has been claimed that when large amounts of salicylates are given day and night a favorable effect is exerted on the course of the disease and cardiac complications can be prevented This is denied by others There is no doubt that the doses of sodium salicylate which were formerly administered were often too small Large doses are more beneficial It has been claimed that the quick relief of inflammation and pain in the joints is due to the fact that salicylates stimulate protein catabolism and alter the water content of the cells (Reid et al)

Intravenous administration has been repeatedly recommended in order that a high therapeutic blood level be reached To be sure it is not always easy to maintain or even reach a high blood level without such untoward effects as tinnitus deafness diarrhea headache nausea or vomiting Occasionally these complaints disappear despite continuation of treatment Dizziness mental confusion and disturbances of vision or breathing (Kussmaul s respiration) may appear Since larger doses are employed more often instances of salicylate poisoning are being reported more frequently in medical literature (Troll and Menten)

Hypoprothrombinemia is observed during the administration of large doses of salicylates particularly if more than six grams are given daily If hemorrhage occurs preparations of vitamin K should be given

Salicylates are said to inhibit the spreading effect of hyaluronidase Like aminopyrine they affect enzyme reactions

The combination of salicylates with sodium bicarbonate for oral administration may diminish gastric irritation This has been said to prevent the attaining of a high salicylate level in the plasma However this finding has not been confirmed Other salicylate preparations and magnesium carbonate in place of sodium bicarbonate have been recommended but these compounds have not been tried on a sufficiently wide scale to form a sound judgment

Sodium salicylate can be replaced by acetylsalicylic acid (aspirin) the dose of both compounds is identical To avoid side effects others recommend an aspirin dosage 3/4 of the dose of salicylates and double the amount of sodium bicarbonate Sodium is to be avoided in heart failure It is important to administer these compounds every four hours day and night in the amount of 0 15 Gm per kilogram in twenty four hours This dose is reduced if deafness tinnitus or nausea appear In the case of nausea and vomiting sodium salicylate can be given rectally in an amount of 4 to 5 grams in 150 ml of warm starch water Stolzer recommends 60 mg of aspirin per pound body weight for two days then 40 mg /lb for the third to seventh day and 30 mg /lb from the eighth day on Instead of sodium salicylate one may administer sodium gentisate which is a metabolic product of the former The dosage is identical

Because of the appearance of the rebound phenomenon this treatment is not discontinued suddenly doses are gradually diminished when all signs of activity have disappeared The shortened sedimentation rate during therapy with salicylates (or ACTH or cortisone) is not always a sign of improvement but is accounted for by the inhibition of production of fibrinogen and globulin in the liver

Parely patients either are refractory to salicylate therapy or display untoward symptoms even when relatively small amounts are administered For these cases aminopyrin (Pyramidon) has been repeatedly recommended Doses of 2 to 5 grams daily have been given over long periods without the development of toxic symptoms This treatment carries with it the risk of agranulocytosis If frequent determinations of the white blood cell count are carried out to detect the early onset of this rare complication no danger is involved Untoward accidents are more common during the administration of cincophen derivatives which are rarely used in acute rheumatic fever

The administration of sulfonamides *in the treatment of active rheumatic* fever is abandoned Penicillin is given in the amount of 600 000 units daily in the beginning for one week in order to eradicate infections with streptococci Then one injection of bicillin is given monthly (see below) No particular success has been observed from the administration of antistreptococcic sera and vaccines In patients sensitive to penicillin one of the broad spectrum antibiotics is indicated

ACTH and cortisone The administration of pituitary adrenocorticotropic hormone (ACTH) and of adrenocortical hormone (cortisone) in patients with rheumatic fever in the active stage has a profound influence on the process Within 1 to 2 days the fever subsides the toxemia disappears arthralgia is relieved the sedimentation rate slowly becomes normal a pericardial effusion

is absorbed tachycardia disappears and even the rheumatic nodules vanish in a few weeks These effects however are rarely lasting and discontinuation of the administration of these compounds in most cases is soon followed by reappearance of activity

As with the administration of salicylates here also the discussion continues on whether the illness is actually shortened by these compounds or whether complications are prevented It seems that this may be the case if treatment is started very early although the same has been claimed — without proof — for salicylates as well

There is no doubt that in certain cases these hormones may be lifesaving This is especially true in juvenile patients with advanced cardiac failure that does not respond at all to standard therapy Here the administration of cortisone or ACTH may lead in the first few days to an aggravation of the condition because *of sodium and water retention Nevertheless marked improvement soon takes* place Even if cessation of therapy leads to the reappearance of signs of congestive heart failure this can be relieved by the same compounds indeed it is often possible to carry the patient over a critical period in this manner Pretreatment with cortisone before mitral surgery diminishes the incidence of histologic signs of activity

Cortisone has the advantage of being active even if given orally but ACTH has a more prolonged effect Two tablets of cortisone acetate of 25 mg are given four times daily or 120 units of ACTH are injected daily (3 injections of 40 units each) In some patients this therapy is tolerated for six to eight weeks For prolonged treatment the daily dose of cortisone in men should not exceed 50 mg and in women 30—40 mg

According to Stolzer cortisone is given intramuscularly in a dose of 300 mg on the first day 200 mg daily on the second to fifth days and 100 mg daily up to the thirty fifth day and 75 mg daily from the thirty sixth to forty second day Smaller doses are needed when the newer stronger similar compounds are given

In children one starts with 80 units of ACTH on the first day followed by 60 units on the second and 40 units daily after two or three days

Another recommended dosage for corticotropin intramuscularly is as follows on the first to fourth day 120 units daily 100 units daily from the fifth to seventh days 80 units daily from the eighth to fourteenth 60 units daily from the fifteenth to twenty first day and then 40 units daily to the thirty fifth day and 20 units daily until the forty second day

Prednisone (Meticorten) is given in the amount of 75 mg daily in divided doses every 8 hours The therapy is continued for 4 weeks in the same dosage then about 5 mg less daily The total duration of the therapy should last if possible 8 to 12 weeks

The patient should be watched carefully for side effects Among others these are rounding of the face (moonface) with acne and Cushing s syndrome (striae hypertension hyperglycemia and glycosuria sodium and water retention)

hirsutism distention of the abdomen mental depression and psychoses The patient should be kept on a sodium poor diet (less than 500 mg of sodium daily) diuretics should be given and potassium ions in the form of fruit juice or 1 to 3 grams of potassium chloride by mouth daily Occasionally an old tuberculosis becomes activated The compounds in particular cortisone and related compounds (hydrocortisone Meticorten) should not be discontinued abruptly The dose is reduced gradually to avoid rebound effects with fever thrombophlebitis rheumatoid arthritis and pleurisy

Recent comparative studies revealed no superiority of treatment of rheumatic fever with these hormones as compared to salicylates Phenylbutazone cortisone corticotropin sodium salicylate and paraaminobenzoic acid are of equal value so that patient s tolerance for the treatment is of decisive value (Kalliomaki) The question is still open It is possible that further studies will show that early therapy with adequate dosage administered for a sufficient time does prevent cardiac involvement and shortens the illness Less rebound phenomena are observed if cortisone is combined with paraaminobenzoic acid and salicylates Some observers suspect that the modus operandi of salicylates is also via the adrenals

Symptomatic Cardiac Therapy Occasionally it is necessary to treat cardiac complaints and complications symptomatically Although digitalis is administered when the patient shows evidence of passive congestion or cardiac failure it often fails to produce the desired response since the myocardial damage is too far advanced Paracentesis may be necessary for large pericardial effusions At times morphine must be given for a short period to control pain Codeine may be advisable to relieve the cough

Diet During the early period fluids should be administered freely and the diet should be light After the first week high caloric but easily digestible diet is indicated Various vitamins have been recommended although the value is uncertain Large doses of ascorbic acid (100 to 200 milligrams daily) are often recommended There is no proof of a beneficial action of succinic or benzoic acid or for the inhalation of oxygen which has been advocated Treatment of the anemia can be postponed until early convalescence Any of the usual iron preparations (ferrous salts) will suffice

Chorea There is no specific treatment for chorea Bed rest quiet surroundings and sedation may afford relief The use of some arsenical preparation such as Fowler s solution is a time honored procedure While some physicians have failed to observe any good effects from ACTH or cortisone others seem to have employed the drugs with success

After Care Even after signs of activity have vanished patients must be watched carefully for a recurrence The young patient especially is susceptible to a new attack after a cold or a sore throat In general children should not return to school for several months after an attack so that they may be protected against new infections and overexertion Plans should be made for the child to receive instruction after convalescence is well under way It may be difficult

to convince parents of the necessity of prolonged care but emphasis upon the fact that cardiac damage may progress as long as there is any sign of active rheumatic fever helps them to understand the importance of a well ordered prolonged recovery phase

Education It is important to educate parents and teachers about rheumatic fever and its subclinical stages (anorexia loss of weight) in order to aid in the early recognition of reactivation or recurrence

Local Treatment Apart from general therapy there remains the perennial question of local treatment of the joints The use of cradles to lift bed clothing from the affected extremities and fixation of painful joints by splints and similar measures deserve consideration since they add to the comfort The value of heat local application of methyl salicylates and similar agents counter irritation and the like is disputed but sometimes they make the situation more tolerable Sponge baths with a weak alcohol solution should be used daily In very rare cases with extreme distention of a joint and the resultant pain the problem of aspiration of the exudate in the joint may come under consideration Aspiration should be done only with complete surgical asepsis It should be emphasized that this is rarely necessary

PROPHYLAXIS

Recurrences are common and each attack means more damage to the heart Preventive therapy often neglected in the past is therefore of great importance

Tonsillectomy One of the oldest measures to prevent a recurrence is tonsillectomy for tonsillitis often precedes the first and subsequent attacks However the success of this operation is not impressive it has been reported that the number of recurrences is not influenced at all by the operation This limited success might be anticipated since pharyngitis like any other infection with hemolytic streptococcus *may precipitate active rheumatic fever* The operation is justified however in patients with recurrent tonsillitis or evident infection of the tonsils Naturally the operation should never be performed during active rheumatic fever and it should not be done too soon after an acute bout of tonsillitis At least 6 to 8 weeks should elapse between the disappearance of acute tonsillitis and operation A bacteremia following tonsillectomy has been found in 28 per cent of the cases Penicillin should be given (600 000 units) daily for five days pre and postoperatively

Environmental Changes The proposal to isolate children and to prevent contact with others in the same age group (sanatoria or convalescent homes with careful selection of their children) has several advantages but obviously is limited in practical application Another method to prevent recurrences is to have the endangered patient move away from possible sources of infection that is crowded areas Permanent transfer to southern climates is also to be considered but the hardship involved in dislocating families and the expense of moving plus the fact that rheumatic fever does occur in the tropics makes such a procedure difficult

Streptococcal Throat Infections

It is estimated that more than 3 per cent of all patients who have a throat infection caused by hemolytic streptococci develop rheumatic fever It is now known that penicillin therapy instituted very early will markedly reduce the incidence of rheumatic fever even though it fails to prevent it in every instance consequently all streptococcal infections particularly those in children should be treated with antibiotics According to Weinstein in patients with scarlet fever who are treated early with only 15 000 units of penicillin intramuscularly every 3 hours for 10 days rheumatic fever appeared in 7 per cent

According to the recommendation of the American Heart Association in children it is best to give 300 000 units of procaine penicillin with aluminum monostearate intramuscularly and to repeat the injection again after three and six days In adults 600 000 units of procaine penicillin in oil are injected intramuscularly every third day

For oral therapy children may take tablets of 200 000 adults 300 000 units one hour before each meal and at bedtime i e four times a day Treatment should be continued for 10 days

If the patient is sensitive to penicillin erythromycin can be given 10 milligrams per pound in four divided doses daily for two days and one half this amount daily for the next eight days

Prophylaxis Therapy carried out throughout the year is indicated in all patients who have had rheumatic fever or chorea particularly if a valvular lesion developed One should start soon after the diagnosis of rheumatic fever is made

Penicillin is given twice daily orally in the form of a tablet containing 200 000 units before breakfast and preferably an hour before meals The injection of 1 200 000 units of benzathine penicillin G (bicillin) once a month is highly recommended but allergy or local pain often prevent this therapy Lozenges or troches of penicillin should not be employed Sulfadiazine in the amount of 1 gram may be given every morning but this should not be employed if the patient has any evidence of allergy Gantrisin is also effective Rashes sore throats and leukopenia necessitate immediate interruption of this form of therapy

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Chapter 11

Bacterial Endocarditis

Bacterial endocarditis may be divided into acute and subacute forms but the distinction is often arbitrary Patients whose illness does not last over six to eight weeks are assigned to the acute type In this form the picture is invariably that of sepsis In the subacute variety septic phases may appear but weeks or even months may elapse before evidence of more than slight infection and bacteremic stages are encountered The introduction of penicillin changed these clinical syndromes and early treatment cures most cases of the acute and subacute type quickly There is however a much more potent reason for separating the acute and subacute forms acute bacterial endocarditis usually involves healthy hearts as a complication of general sepsis while subacute bacterial endocarditis (or endarteritis) is a disease involving abnormal hearts or vessels Actually the duration of both acute and subacute bacterial endocarditis may be the same and another term for these conditions would seem desirable

Acute Bacterial Endocarditis

Etiology This lesion also called malignant or ulcerative endocarditis is an infection caused by highly virulent microorganisms It may accompany any type of sepsis pneumonia osteomyelitis puerperal fever or sinus thrombosis The causative agents are hemolytic streptococci staphylococcus albus and aureus pneumococci gonococci and influenza bacilli Sometimes the colon bacillus or the meningococcus is found Among 44 cases of acute bacterial endocarditis hemolytic streptococci were found in 21 staphylococcus aureus in 11 bacterium coli communis in 5 and gonococci in 2 Two other patients had meningococcus infections one staphylococcus albus and two a mixed infection (Phipps) The bacteremia is not always demonstrable

Pathology Sometimes the valvular vegetations are small and are arranged like those of rheumatic endocarditis more often they are large and irregularly arranged The favorite sites of development are the atrial aspect of the mitral and tricuspid valves or the ventricular side of the aortic valves The large thrombi are composed of clumps of bacteria between layers of fibrin and leukocytes The vegetations may appear on a normal valve or on one previously diseased If multiple the vegetations may attain a diameter exceeding 1 cm and in this instance they may render the orifice stenotic The firmly attached vegetations usually have a friable lobulated surface With necrosis of the valvular tissue an

ulcer forms with a shaggy base covered by a clot If the ulceration penetrates a leaflet aneurysm or perforation may follow

Symptoms Signs The clinical picture can hardly be separated from that of sepsis Irregular chills sweating high widely fluctuating fever extreme malaise headache and anorexia prevail in the symptomatology Very often the participation of the heart in the process is not discernible for the cardiac manifestations (tachycardia and a systolic murmur) stand in the background in comparison to the signs of sepsis Owing to the stormy course of the disease there is rarely time for the formation of valvular alterations capable of producing diastolic murmurs The latter alone would establish cardiac involvement The spleen is often enlarged and sometimes tender Sooner or later petechiae appear in the skin or conjunctiva The white blood cell count may be increased to 30 000 The urine shows albumin and red blood cells Not infrequently embolic occlusion of a large vessel in the spleen kidneys brain mesentery or extremities rapidly changes the picture

Acute bacterial gonococcic endocarditis in previous years was not rare One author found it in 26 per cent of all his patients with acute and subacute bacterial endocarditis in the preantibiotic era Acute nephritis and uremia are frequent complications Pneumococcic endocarditis which often involves the valves of the right heart was rapidly fatal The pulmonic valves occasionally are affected in other forms of bacterial endocarditis

The progressive anemia leukocytosis the course of the disease and its complications are the same as those of sepsis

Prognosis In the past the disease usually has been fatal and cases with evidence of healing were only rarely encountered Instances of healing even of gonococcal endocarditis have been reported but these were rare as indicated At the present time with the general use of antibiotics most patients including those who suffer from septicemia caused by meningococci or staphylococci are saved Therapeutic problems however do arise when the agent (staphylococci) does not respond readily to the antibiotics or when the illness is recognized too late

Therapy Penicillin is the antibiotic of choice in most cases With meningo coccal sepsis sulfonamides are more useful The other antibiotics are used according to specific indications (see below)

SUBACUTE BACTERIAL ENDOCARDITIS

Subacute bacterial endocarditis (endocarditis lenta) has been separated from acute bacterial endocarditis chiefly by virtue of its prolonged course and certain features resulting from this time factor and the nature of the etiologic agent The patient developing subacute bacterial endocarditis already has an acquired or congenital cardiac abnormality After World War II an increased incidence of this disease was observed in countries where widespread malnutrition was rampant

Etiology and Pathogenesis The causative agent in over 90 per cent of the cases is *streptococcus viridans* which is an organism of low virulence This group of streptococci can be subdivided into several strains Of special importance is the most common causative agent the streptococcus salivarius which responds readily to penicillin treatment another streptococcus fecalis (enterococcus) is a normal inhabitant of the human intestines In rare cases hemolytic streptococci meningococci influenza bacilli staphylococcus aureus and albus diplococcus pneumoniae Escherichia coli Salmonella Neisseria catarrhalis streptobacillus moniliformis Bacillus proteus Pseudomonas aeruginosa and even gonococci — all agents usually responsible for the acute type of bacterial endocarditis — may produce the subacute form when the virulence of the provocative agent is low In rare cases streptothrix candida albicans and members of the Brucella group are etiologic factors Occasionally two or even three microorganisms have been found simultaneously

Under normal conditions blood plasma and leukocytes destroy the streptococcus viridans quickly even when large numbers are injected intravenously fibrin however which is soon deposited on affected endothelium and endocardium protects the microorganism from destruction Blood is bacteriocidal only for organisms free in the circulation In subacute bacterial endocarditis the body seems biologically immune to the infectious agents in contrast to the hypersensitive reactions of the connective tissue to hemolytic streptococci in rheumatic fever

PREVIOUS CARDIAC CONDITIONS It is very unusual for a subacute bacterial endocarditis to develop in a healthy heart Even if the valves occasionally seem normal on gross examination histologic sections usually reveal new or old rheumatic changes In a vast majority of cases an old rheumatic valvular lesion is present In this respect the mitral valve is involved a little more commonly than the aortic valve Not rarely subacute bacterial infection is superimposed upon a congenital heart lesion especially on a patent ductus arteriosus a ventricular septum defect or coarctation of the aorta In rare cases the disease develops on the basis of a syphilitic aortitis or atheromatosis

The cardiac malformations which form the basis for subacute bacterial endocarditis sometimes are too trifling to produce any clinical symptoms or signs Thus the disease may develop in patients with bicuspid aortic valves of a congenital type (bicuspid valves are occasionally the result of a former rheumatic infection) or on a malformed pulmonic valve

Of interest is the discovery of subacute bacterial endocarditis in the dog as the result of strain Mural and valvular vegetations were observed after the creation of a large arteriovenous fistula in dogs and were also seen clinically in this condition (Lillehei Parmley et al) presumably because of the combination of stress and infection Subacute bacterial endocarditis was found in a patient with mitral regurgitation caused by rupture of a papillary muscle which resulted from myocardial infarction (Leman) in mural thrombi following myocardial infarction (Joffe and Feil) and after endocardial trauma in connection with

cardiac catheterization Bacterial endocarditis may appear during treatment with ACTH owing to diminished resistance In arteriovenous fistulas the focus spreading the infection was occasionally the fistula itself and the patients were cured by its extirpation

Evidence of active rheumatic fever is found in an astonishingly high percentage of patients with subacute bacterial endocarditis Some pathologists have found activity (presence of Aschoff bodies) in most of their patients with rheumatic heart disease who succumbed to subacute bacterial endocarditis The streptococcus viridans infection is often implanted on a fresh rheumatic valvulitis The disease seems to follow various infections which erode the endothelium and produce deposits of fibrin

Trauma and contamination suffice Streptococci of the viridans type are often present in the blood one wonders as Sir Thomas Lewis did why subacute bacterial endocarditis does not occur more frequently

An experimental form of the disease can easily be provoked by creating a valvular lesion and injecting streptococcus viridans into the blood stream The mechanical factor in its appearance is demonstrated by the fact that the lesion develops on that part of the valve which is most exposed to mechanical irritations In a patent ductus arteriosus the lesion occurs in the wall of the pulmonary artery where the blood forced by aortic pressure through the duct strikes the wall of the artery in a patent ventricular septum the lesion develops in the right ventricle at the point where blood is forced through the septal defect and in coarctation of the aorta it is found near the stenotic isthmus In the cases of patent ductus arteriosus and aortic coarctation we are of course dealing with an endarteritis rather than an endocarditis

PORTAL OF ENTRY The most frequent portal of entry is the upper respiratory tract after which comes the urogenital system otitis and wound infections Not rarely subacute bacterial endocarditis follows a perfectly normal delivery

There is a frequent opportunity for implantation of streptococci in areas with damaged endothelium since blood cultures often reveal the presence of streptococcus viridans in patients without subacute bacterial endocarditis In rheumatic fever nonhemolytic streptococci are found in almost 10 per cent (Lichtman and Gross Swift and Kinsella) Streptococcus viridans bacteremia is common after irritation of foci of infection — after massage of infected gums or tonsils for example Among 138 patients who had teeth extracted a transitory bacteremia due to nonhemolytic streptococci was found in 60 9 per cent the incidence was even higher (75 per cent) in patients with a chronic mouth infection Among 110 patients with a septic mouth streptococcic bacteremia was found in 10 9 per cent in a single examination irrespective of any operative procedure (Okell and Elliott) In another study (Palmer and Kempf) one or two teeth were extracted in 82 patients and streptococcus viridans bacteremia followed in 13 4 per cent The clinical experience that subacute bacterial endocarditis frequently follows extraction of teeth upper respiratory tract infections tonsillectomy and puerperal infections is in accord with these results Nonhemolytic streptococci are likewise

found in the blood after a curettage or after a simple surgical operation such as an appendectomy Bacterial endocarditis may follow genito urinary manipulations (Beattie) or cardiac surgery (Kowan and Nahas) From all data now available it seems that infection of the blood stream is a common event and gives opportunity for streptococci to invade a locus minoris resistentiae in the heart Staphylococci are often found in the blood of patients who suffer from osteomyelitis and in drug addicts who give themselves injections of morphine or heroin without the necessary precautions

Age The disease is observed at all ages having been reported in infants as well as in patients over 80 years old It is not common in children however

Incidence It is difficult to evaluate the incidence of the disease Apparently subacute bacterial endocarditis complicates about 5 per cent of rheumatic heart lesions In two Boston hospitals Gelfman found subacute bacterial endocarditis in 25 per cent of patients with rheumatic heart disease This figure does not reflect the true incidence of the disease in congenital heart lesions it is much higher

Pathology Ulcers and thrombotic vegetations form on the affected valve on the endocardium or in an artery The vegetations consist of remnants of blood platelets white and red blood cells microorganisms and great masses of fibrin and vary in size color and consistency They may be small and nodular or they may form large irregular club shaped friable masses The pedunculated formations are often firm and contain fibrous tissue or calcium deposits as evidence of a tendency to heal

The vegetations may be large enough to obstruct the flow of blood Valves may be perforated and chordae tendineae may rupture At times mycotic aneurysms occur in various vessels but they are especially prone to develop in the aorta the arteries of the brain and the heart and in the extremities Presumably they are the result of infected emboli lodging in the vessel wall Embolism may occur anywhere and not rarely causes death If the right heart is involved (in patients with ventricular septal defects) pulmonary embolism is frequent Embolic or diffuse hemorrhagic nephritis is common Acute myocarditis with hemorrhages and minute infarcts also occurs regularly (Saphir)

In all stages there may be bacteria free periods with negative blood cultures and according to some observers no organisms in the vegetations

Symptoms In many cases the disease begins insidiously with very vague and indefinite initial symptoms such as general malaise cough loss of weight transitory arthralgia fatigue loss of appetite sweating aches and pains in various parts of the body At times the onset is associated with a cold or a sore throat Under these circumstances the physician may not be consulted until much later months may elapse before the situation is regarded more seriously In other cases the disease begins as a polyarthritis and resembles rheumatic fever clinically only gradually does the picture of subacute bacterial endocarditis become evident A sudden chill hemiplegia or pain in the finger tips and toes caused by small emboli are the factors that impel some patients to summon a

physician and seek help Often intolerable abdominal pain indicates embolism of the spleen kidney or intestine

In many cases patients are free from complaints and are even euphoric If the fever were not present I would be well is a commonly heard statement

Signs While there is no characteristic single sign of subacute bacterial endocarditis the syndrome is so typical that the fully developed disease is easily recognized At the beginning the diagnosis is difficult and errors are committed in two directions Not rarely the unwarranted diagnosis is made on the basis of fever and a heart murmur in patients who are later discovered to be suffering from pyelitis or some other febrile disease Errors are also made in failing to consider the possibility of subacute bacterial endocarditis from the start a mistake the patient s family rarely forgives

The temperature may show all variations from a slight elevation to a septic intermittent or remittent curve with chills The fever may disappear completely for weeks and even for months

The heart rate is usually not abnormally rapid Arrhythmias are uncommon for subacute bacterial endocarditis usually develops in a compensated heart without evidence of congestion Myocardial inflammatory lesions are often present and decompensation which may occur in the course of the disease necessitates the use of digitalis

Inspection usually shows a yellow muddy (cafe au lait) discoloration of the pallid skin coincidental with a secondary anemia This secondary anemia may become a very prominent feature as the disease progresses The fingers are often clubbed Few diseases manifest such rapid development of this change Since this sign is very rare in uncomplicated rheumatic valvular disease the presence of clubbing in a febrile cardiac patient should immediately arouse the suspicion of subacute bacterial endocarditis

In a majority of cases cardiac examination reveals the typical features of a rheumatic or congenital heart lesion Occasionally the cardiac involvement is too slight to produce signs detectable by auscultation or percussion but such cases are rare Murmurs change in intensity new murmurs appear or murmurs which were present for years vanish This is because large vegetations may obstruct an orifice close a deficiency in the interventricular septum or close a patent ductus arteriosus

Petechiae often appearing in crops develop in the neck under the nails above and below the clavicle around the inner malleolus and on the conjunctiva and the soft palate They result from hemorrhage caused by small bacterial emboli in capillaries Often they have a white center due to a minute necrosis created by the embolus Splinter hemorrhages under the nails with or without this white center are not pathognomonic for they may occur in various infections and are not rare in generalized lupus erythematosus

Osler nodes are very tender pea size nodules which appear in the finger tips toes (often under the nails) and on the vola manus and planta pedis They cause local swelling and their tenderness may distress the patient for several days

According to most observers the nodes as well as the petechiae derive from emboli Others attribute them to a proliferative arteritis The skin over the affected area appears red or a redness shimmers through from the deeper parts The pain disappears in a few days and only a purple spot remains for a while The picture is modified if deeper or more superficial arteries are involved Janeway lesions are maculae or papulae not painful 1 to 4 mm in diameter appearing on the palms or the soles of the feet

Purpura occurs rarely

The spleen is enlarged and hard in about 55 per cent of the cases The enlargement is greatly accentuated by embolisms to this organ If embolism occurs late the spleen may not be palpable for several months

Laboratory tests Laboratory examination reveals a positive blood culture in 75 to 90 per cent of the cases Since as pointed out earlier nonhemolytic streptococci are not rarely found in the blood in other conditions such as rheumatic fever rheumatoid arthritis and dental infections three or four positive blood cultures should be secured if possible to verify the diagnosis On the other hand one or more negative reports do not eliminate the possibility of subacute bacterial endocarditis for the disease may be associated with negative blood cultures over a considerable period of time The incidence of negative blood cultures is reduced by the taking of fairly large amounts of blood for culture At least 20 ml of blood *should be drawn and on the first day a culture should be taken every hour for five* hours One should always employ both plates and broth cultures The best time to withdraw the blood is when the patient s temperature is rising or during a chill It is reported that the incidence of positive blood cultures is higher from bone marrow aspirations Instances are known however in which cultures were negative from the bone marrow and positive from venous blood Arterial blood has no advantage over venous blood The growth of some nonhemolytic streptococci may not be visible before three weeks

From 140 patients with nontreated subacute bacterial endocarditis Griffith and Levinson obtained 129 positive cultures on the first day of hospitalization 8 positive ones on the second day and only 3 on the third day In this connection it is important to note that less than 3 per cent of the patients who failed to show a positive blood culture on the first two days showed one later The culture is often sterile in subacute bacterial endocarditis within the right heart

In 46 per cent of 135 blood cultures Loewe and Alture Werber found a streptococcus with a distinctive combination of properties which the authors called streptococcus s b e It was the causative organism in 40 of 68 subjects with subacute bacterial endocarditis Standard dosage of penicillin often is not sufficient in these patients and the disease recurs

In every instance an anaerobic culture should be made Penicillinase should be used whenever the patient has received penicillin about 24 hours prior to withdrawal of the blood

Sensitivity tests measuring the inhibition of growth of the responsible agent by different antibiotics should be done if possible More than 90 per cent of all

strains of streptococcus viridans are inhibited by 0 01 to 0 1 units of penicillin per cubic centimeter

Usually there is a moderate increase of sedimentation rate A hypochromic anemia is common and often is progressive The white blood cell count does not change characteristically but a polymorphonuclear leukocytosis may be present However leukopenia can also occur Large phagocytic cells are occasionally seen in the blood smear The Wasserman reaction may be positive in the absence of syphilis

Electrocardiogram The electrocardiogram affords no diagnostic help Changes may appear and are to be expected in view of the frequent alterations of the myocardium but they are not characteristic Extrasystoles and atrial fibrillation are rare

Urine The urine shows a great number of red blood cells in many cases and even gross hematuria The latter may temporarily increase after renal infarction In the intervals between renal infarctions albumin hyaline and granular casts are observed

Duration This varies greatly since the course may be suddenly interrupted by a lethal cerebral embolus or the disease may assume a very protracted character and last for more than two years When the patient succumbs to a complication early in the course the diagnosis is often missed Long bacteria free intermissions with relative well being are also encountered

Complications Most of the complications are due to emboli or to mycotic embolic aneurysms The damage caused by emboli depends upon the location and size of the occluded artery and the frequency with which embolism recurs Their appearance cannot be predicted or prevented Cerebral emboli may cause hemiplegia or paresis Renal embolism is responsible for severe backache and hematuria embolism of a coronary artery may produce myocardial infarction with prolonged anginal pain as seen in coronary thrombosis Valvular thrombi cause obstruction and valvular ulcerations cause perforations Perforation of the heart may follow an abscess of the ventricular wall If the endocardial thrombi are situated in the right ventricle (as happens in an interventricular septal defect) pulmonary emboli are released and simulate the picture of a pneumonia Generally embolism causes a rise of temperature leukocytosis and increase of the sedimentation rate It should be emphasized that an embolism may occur months after the illness seems to be under control as the result of antibiotic therapy

Pericarditis occurs occasionally A subarachnoid hemorrhage may be the first sign of the disease Emboli in a peripheral artery may cause gangrene A splenic abscess may follow embolism of this organ and may rupture into the peritoneal cavity causing peritonitis

Mesenteric infarction and intestinal gangrene are occasionally observed

Uremia due to nephritis terminates the scene in a large percentage of cases The nephritis may be diffuse acute or subacute Lohlein s embolic nephritis may exist

Sometimes psychoses appear that may be connected with anatomic changes in the nervous system There is also severe headache double vision and meningeal signs caused by embolisms signs of brain abscess occur Subarachnoid hemorrhages occur because of rupture of mycotic aneurysms

Differential Diagnosis Any unexplained fever particularly in a cardiac patient whatever the age speaks in favor of subacute bacterial endocarditis The differentiation from rheumatic fever is especially difficult since both may be present simultaneously and the diagnosis of subacute bacterial endocarditis is often missed in these cases because the physician fails to consider its presence One of the most common conditions wrongly diagnosed is grippe or viral infection

Prognosis The outlook in this disease became brighter with the advent of intensive antibiotic therapy

In rare cases spontaneous recovery is possible Distinct healing processes with scar formation and even lime salt deposits have been observed at necropsy According to some estimates these spontaneous recoveries occur in 1 to 3 per cent of all diagnosed cases The latter figure is in our opinion too optimistic at least if the fully developed cases alone are taken into consideration But cases with a mild infection that run a benign course do occur they are more prone to spontaneous cure and respond better to treatment They occur more often among the cases with congenital abnormalities One must be cautious in pronouncing a patient cured for remissions may last as long as six months The prognosis is undoubtedly better for these cases where combined penicillin therapy and surgical intervention are applicable as in patent ductus arteriosus or an infected arteriovenous fistula

The incidence of cures approaches 80 per cent if all cases of subacute bacterial endocarditis are considered but in bacteremia with staphylococci it drops to 52 per cent Patients die from complications such as emboli and cardiac failure even after the endocarditis is cured

Therapy Therapy starts with prophylaxis Oral sepsis must be treated carefully infected teeth and tonsils should be removed

In view of the frequent occurrence of temporary bacteremia after dental extractions or tonsillectomy antibiotics are administered prophylactically for a few days before and after tooth extraction The same method is employed for five days after delivery

The treatment of subacute bacterial endocarditis should start as soon as the diagnosis is made One should not wait for weeks until a positive blood culture is obtained since irreparable damage may be inflicted in the interim by the myocarditis or embolism It is better occasionally to treat a patient without absolute proof of the diagnosis than to wait too long

When the diagnosis is suspected five blood cultures should be taken at hourly intervals and therapy should be started immediately after It should be remembered that persistently negative cultures are not rare

The recent findings that penicillin penetrates fibrin and that it persists in tissue fluids much longer than in the blood (as well as the general availability of this antibiotic) make it the remedy of choice

In 95 per cent of the cases the administration of 2 000 000 units of penicillin daily for a few weeks is sufficient to cure the patient In some cases smaller doses suffice but one can never predict this in advance If sensitivity tests are available early one chooses a dose which is 4 to 5 times higher than that required to inhibit the causative agent in vitro Sometimes sensitivity may be high in vitro but not in vivo Most nonhemolytic streptococci are sensitive to 0 1 unit of penicillin per cc or less Enterococci may be sensitive to 1 to 5 units Experience with the sulfonamides has shown that pure inhibition does not suffice to cure the disease

We recommend starting with the administration of 600 000 units of procaine penicillin (three times a day Others recommend the administration of penicillin (500 000 U every three hours If cardiac failure is present the potassium salt is preferred This makes greater peak levels than repository penicillin and fibrin deposits are penetrated better It is important to note (Eagle et al) that if the concentration of penicillin in the blood exceeds a certain level the effect is no greater than at a lower level In the intervals between injections when the level of penicillin falls the bacteria do not multiply and many damaged microorganisms are disposed of by the body

In most cases the fever subsides in a few days an unusual sense of well being is experienced by the patient the appetite improves and the heart rate becomes slower When all signs of activity disappear we continue the same dose for three more weeks Cultures if positive at the beginning are taken repeatedly even if the fever subsides a positive culture may indicate that the dose is insufficient One should bear in mind that fever may be due to the presence of active rheumatic fever the absorption of abnormal diseased foci to embolism or sensitivity to penicillin In the latter case another penicillin is used (penicillin O instead of penicillin G) which is antigenically different

If there is no clinical evidence that the disease is becoming arrested or if the culture persists positive the dose is increased Daily doses up to 100 million units have been found necessary and have been given with success

If enterococci are found one starts with 10 to 20 million units daily and adds twice daily an intramuscular injection of 1 gram of a mixture of streptomycin and dihydrostreptomycin In these cases penicillin is also administered intravenously in doses of 500 000 units or more every two hours If the microorganism is susceptible the dose may soon be reduced The combination of penicillin with other antibiotics has been claimed to reduce the activity of penicillin but this does not hold for streptomycin In staphylococcic endocarditis a combination of penicillin with erythromycin (3 to 4 grams daily intravenously) or bacitracin may prove successful Sometimes bacitracin alone cures the endocarditis provoked by gram positive bacteria 100 000 units are given daily one third or one fourth of this amount in each dose intramuscularly Nephrotoxic effects have been reported

Terramycin and Chloromycetin given alone seem merely to exert bacteriostatic effects In some instances successes have followed the use of dihydrostreptomycin combined with Terramycin Neomycin sulfate intramuscularly may help in staphylococcic endocarditis there is danger of injuring the acoustic nerve but this risk must be taken in a disease which is so serious The danger is not great if only one gram (of neomycin) is given daily for 10 days Usually 0 25 Gm is injected every 6 hours In infections with proteus or pseudomonas aeruginosa one must administer polymixin B in spite of potential renal damage This danger has been lessened by newer preparations One administers 100—200 mg daily intramuscularly divided into four doses These compounds are often lifesaving In the endocarditis of brucellosis the combination of Aureomycin with dihydro streptomycin has proved useful infections with bacillus influenzae and para influenzae may be treated with the same mixture or with Terramycin in place of Aureomycin Laboratory sensitivity tests are decisive for the choice of the antibiotic

It is of interest that 65 per cent of the patients who died when the endo carditis seemed controlled had viable microorganisms in the valves Therefore in advanced long standing disease it is well to continue therapy for more than three weeks after clinical improvement is established

For the first three or four weeks the patient must rest in bed but in the last few weeks he may be up and about provided no exertion is undertaken The circulation must be watched since myocardial damage often leads to heart failure

In order to increase the blood level of penicillin by preventing its rapid excretion by the renal tubules simultaneous administration of other agents has been recommended Caronamide seems effective 1 5 to 2 0 Gm are given every four hours Benemid diotrast paraminohippuric acid have also been employed Benamide (Probenecid Baker and Pilkington) is usually well tolerated and preferred One half gram is given every 6 hours In most cases these drugs can be omitted

After the illness seems cured the patient is advised to watch his temperature every two hours one day a week for a year so that therapy is started early if the disease shows evidence of recurrence Such recurrences are not rare Often it is difficult to decide whether a recrudescence or reinfection has occurred

Short term therapy in various forms has been recommended In one investi gation 600 000 units of aquous penicillin was given every 6 hours with a mixture of 1 0 Gm of equal parts of streptomycin and dihydrostreptomycin (Combistrep or Distrycin) intramuscularly (If not more than 2 grams of the mixture are given daily for not longer than 4 weeks vestibular damage (streptomycin) and auditory nerve damage (dihydrostreptomycin) occurs rarely) This was continued for five days the injections were then given at 12 hour intervals (Hall et al) In a certain percentage of cases this short term therapy is sufficient the type in which success will be secured cannot be foretold Therefore prolonged therapy with moderate dosage seems better than short term method

TERMINAL (CACHECTIC) ENDOCARDITIS

The small valvular vegetations in rheumatic endocarditis should not be confused with similarly located small thrombi seen occasionally along the closure line of the mitral and aortic valves in cachectic patients suffering from cancer uremia leukemia and other wasting diseases

These thrombi may reach the size of a pea and in rare instances are even larger They do not contain much fibrin but are composed mainly of amorphous masses derived from blood platelets The finer mechanism of their formation is unknown They are nonbacterial but may be invaded by microorganisms just before death

Careful histologic examination of valves showing this type of endocarditis may disclose evidence of an old rheumatic infection occasionally terminal endocarditis is superimposed on an atherosclerotic process of the valve

Patients showing this type of endocarditis not rarely have thrombosis of the systemic veins (Grant) they may even present the clinical picture of migratory phlebitis

The process is not always terminal Healing is possible if the patient recovers from the associated chronic cachectic disease Because there is no evidence of inflammation the term degenerative verrucal endocardosis has been proposed (Allen and Sirota)

ENDOCARDITIS IN GENERALIZED LUPUS ERYTHEMATOSUS

Etiology The etiology of this interesting lesion known for many years only as a skin affection is obscure It seems to be allergic in origin and belongs to the group of so called collagen diseases Sunlight may aggravate the proce s The resemblance to other forms of lupus is rather remote Over 80 per cent of the cases are encountered in women before the menopause although no endocrine factor has been demonstrated

Of great importance is the finding of L L (lupus erythematosus) cells that is large polymorphonuclear cells containing nuclear debris in the blood and bone marrow in rare cases they are also found in the pericardial fluid They result from the phagocytosis of free nuclear material from another leukocyte of the same type The cells are found in 96 per cent of the cases A negative test does not militate against the diagnosis False positive tests are exceedingly rare

Pathology The collagenous fibers all over the body are affected and degenerative necrotic lesions appear in the kidney skin and heart

The endocardium is involved in about 30 per cent of the cases (Libman and Sacks) Verrucae appear on both sides of the valve but not at the line of closure and mural vegetations often develop on the atrial endocardium Vegetations may also develop between the papillary muscles particularly in the right heart These changes were originally described as atypical or indeterminate endocarditis There is evidence of myocardial degeneration with interstitial infiltration and exudate *The pericardium and pleura are often involved in a fibrinoserous inflammation* Bronchopneumonia is common In the kidney a peculiar thickening of the capillary walls called wire loop changes is characteristic The skin lesions

are not pathognomonic on microscopic examination and consist of a cellular infiltration into the corium The vascular lesions are composed of capillary dilatation proliferation of the endothelium and necrotizing inflammation sometimes with thrombosis of the smaller arteries No Aschoff bodies are found and no bacteria are demonstrable in the tissues

Symptoms Signs The disease often begins insidiously with low irregular fever joint pain weakness and loss of weight A lymphadenopathy is often found Typical leukopenia is usually associated with progressive anemia and thrombocytopenia Albuminuria is common Often there is a skin eruption consisting of disc like patches with raised red edges and depressed centers When the covering desquamates dull white scars are left behind These lesions may be seen on the hands feet ears or chest in their most typical form they merge to form a butterfly pattern over the nose and on the cheeks The cutaneous signs may be outstanding but in some cases they are absent They may appear after sunburn or the use of ultraviolet light or x rays The electrocardiogram may show abnormal T waves in many or all leads

False positive serologic tests for syphilis are obtained

Physical examination of the heart shows nothing characteristic A systolic murmur may be audible and is without significance Evidence of pleural or pericardial involvement may be obtained

Therapy Cortisone (150 to 200 mg) daily or ACTH (50 to 150 mg) often arrest the illness and in a crisis may bring about improvement in 24 to 48 hours While some observers claim this improvement does not increase life expectancy others believe that the patient may be kept alive for an indefinite period (Soffer et al) After improvement the dose is reduced sometimes doses as small as 5 milligrams of ACTH daily suffice All the precautions necessary in connection with this therapy must be observed

Recently prednisone and prednisolone which are said to be four times as potent as cortisone are used in lupus erythematosus As the initial suppressive daily dose Bollet et al recommend 20 to 60 mg usually 30 or 40 mg daily as a maintenance dose 18 mg were given daily Effectiveness and limitation of therapy with these drugs are the same as with cortisone and corticotropin

RARE TYPES OF ENDOCARDITIS

Tuberculosis may cause an endocarditis in which tubercle bacilli are demonstrable in the valvular vegetations (Davie) This endocarditis in not unusual in miliary and disseminated tuberculosis and it does not affect the closure line of the valves (Baker)

A variety of organisms have been recovered from the valves including Brucella abortus and organisms such as actinomyces other fungi are also known to produce a mycotic endocarditi

In exceptional cases other agents e g erysipelothrix the causative agent of swine erysipelas causes endocarditis in man Loeffler described in endocarditis parietalis fibroplastica with eosinophilia (up to 70 per cent) in the blood

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Chapter 12

Valvular Lesions

Insufficiency of the Aortic Valves

Incidence

Insufficiency of the aortic valves commonly but somewhat incorrectly called aortic insufficiency or aortic incompetence is one of the most frequent isolated valvular lesions It is most prevalent in males The rheumatic type is usually combined with an aortic stenosis and often also with a mitral stenosis of the same origin In recent years the incidence of syphilitic aortic insufficiency has been greatly reduced

Etiology

Rheumatic Fever and Syphilis The high incidence of the lesion is readily appreciated because both rheumatic fever and syphilis are responsible for deformities of the aortic valves which render them incapable of proper closure and permit diastolic regurgitation of blood into the left ventricle The valves become thickened deformed and retracted In syphilis the widening of the commissures in addition to shortening of the valve aids in the production of incompetency

Atherosclerosis Formerly aortic insufficiency due to atherosclerotic changes in the valve was a very common diagnosis This was due to the fact that a syphilitic aortic insufficiency was usually mistaken for an atherosclerotic lesion This error is partly explained by the secondary atherosclerotic changes prone to occur in fully developed syphilitic aortitis Although aortitis has been known as a pathologic lesion for several decades its prevalence has been noticed rather slowly by the clinician and pathologist Very often the atherosclerotic process is so pronounced that on gross examination it conceals the underlying syphilitic aortitis making the correct diagnosis possible only in microscopic sections

Since no history of rheumatic fever can be elicited in an appreciable percentage of rheumatic patients and a syphilitic infection is often denied either from ignorance or embarrassment atherosclerotic insufficiency is diagnosed when secondary calcification has taken place in a valve altered by syphilis

Primary atherosclerotic changes of the aortic and mitral valves are however so common that they may even be called physiologic Small yellow spots appear on the aortic side of the aortic valves and on the ventricular surface of the mitral valves that is in places most exposed to pressure this is seen even in patients under ten years of age These spots represent deposits of cholesterol They often

disappear in children but recur and later persist Still later the amount of connective tissue increases small necroses appear and secondary calcification takes place The annulus fibrosus also is often affected The process starts at the base of the valves extends to the free edge and reaches the valvular surface Shrinkage of the connective tissue and calcification disturb the function of the valve and may cause insufficiency

Relative Incompetence Another type known to Corrigan is relative aortic insufficiency It is rare for the valvular ring itself to dilate and to cause incompetency in the presence of a normal valve even with the highest blood pressure values Relative aortic insufficiency is usually the result of marked damage to the myocardium or the aorta (Laubry and Doumer) It has been described in connection with myomalacia consequent to coronary sclerosis in fatty degenerative infiltration from anemia in aortitis without involvement of the valves (Maresch) and in hypertension Although some authors consider it a frequent event (Garrin) in our experience it is rare

Trauma Traumatic aortic insufficiency is also rare It occurs after direct or indirect trauma regardless of whether the valves are normal or abnormal Sudden physical strain in a patient with aortitis and syphilitic valvular changes may rupture a leaflet and lead to the sudden appearance of an aortic insufficiency These patients often present a musical diastolic murmur (sea gull murmur) which may be heard at some distance from the chest wall with the unaided ear The murmur is usually accompanied by a thrill Immediately after the provocative exertion severe pain is felt over the heart and the midsternal region the result of acute cardiac dilatation causing stretching of the pericardium This form of aortic regurgitation like the other types is more common in males It developed in one of our patients during a brawl and in another while he was playing soccer Both had syphilitic aortitis

Marfan s Syndrome In this congenital abnormality of the connective tissue which will be discussed more in detail in the chapter on congenital heart diseases insufficiency of the aortic valves occurs caused by changes in the aortic wall and valvular ring Dissecting aneurysms or rupture of the aorta are common

Symptoms

Paucity of Symptoms Most patients with aortic insufficiency have few symptoms In other valvular lesions especially those of the mitral valves dyspnea and palpitation appear quite early and many times the patient is aware of his cardiac disease long before decompensation occurs Patients with aortic insufficiency on the other hand remain asymptomatic for a long time For this reason the discovery of the lesion is often accidental — in the course of a periodic health examination after application for life insurance or upon examination by Army draft boards Such patients are often fully active they pursue ordinary sports and may even indulge in *strenuous exertion without symptoms* The diagnosis of an organic disease is consequently received with surprise

Freedom from complaints occurs even in patients who exhibit all the peripheral and auscultatory signs of the lesion that is marked backflow through the valve This situation is explained by the fact that the left ventricle is capable of full performance for many years even when increased demands are placed upon it The chief complaint of most cardiac patients is dyspnea Paroxysmal nocturnal as well as exertional dyspnea are absent in aortic insufficiency so long as there is complete compensation by the left ventricle accordingly the lesion is often entirely asymptomatic

Complaints may be absent for decades an aortic insufficiency which appeared after rheumatic fever in childhood may never produce symptoms or may cause them only at an advanced age This good prognosis and long duration of full compensation however are more often seen in the rheumatic type In syphilitic aortic insufficiency the prognosis is much poorer Naturally exceptions do occur we have seen patients with a syphilitic aortic insufficiency whose hearts did not change in size or shape and in whom no symptoms of decompensation appeared for more than a decade

The duration of compensation in any valvular lesion depends to a great extent on the condition of the myocardium and only to a slight degree upon the extent of the valvular lesion Patients with an extreme aortic stenosis or regurgitation may remain well provided the myocardium is normal On the other hand rapid and progressive decompensation takes place despite a minor valvular alteration when the heart muscle is damaged

Although the heart muscle is affected quite regularly in rheumatic fever usually the process is focal and heals completely without causing significant or permanent damage Only in occasional cases does failure set in early In syphilitic aortic insufficiency early myocardial damage is common largely because the orifices of the coronary arteries are narrowed heart failure thus appears usually at an early stage and often before the affected valves become markedly insufficient

Dyspnea The first complaint of patients with aortic regurgitation is as a rule paroxysmal nocturnal dyspnea which is typical for left ventricular failure Exertional dyspnea follows in accordance with the speed with which the left ventricle progressively fails and pulmonary stasis develops

Angina Pectoris A small percentage of cases with aortic insufficiency have real anginal pain It may occur even in children Often the distress develops while the patient is at rest or sleeping at night The pain may be tormenting While it responds readily to nitroglycerin frequently the relief is only temporary In this type of pain a paroxysmal rise of blood pressure has decisive importance The phenomenon will be discussed in the chapter on angina pectoris

Signs

Skin According to some clinicians patients with aortic insufficiency are so pale that the disease can be differentiated at first glance from mitral lesions Such a statement however is not in accord with the facts Patients with beginning

or advanced aortic insufficiency usually look perfectly normal and pallor certainly is not typical for this lesion If the patients are pale the chances are this can be traced to definite causes When the lesion is caused by syphilis a secondary anemia was seen following therapy with mercury or the arsenicals In rheumatic aortic insufficiency pallor may suggest continued activity of the rheumatic fever and therefore the temperature leukocyte count and the sedimentation rate should be checked The possibility of subacute bacterial endocarditis should be borne in mind

Pulse The examination of the patient should begin — as should the examination of all cardiac patients — with palpation of the pulse In a fully developed insufficiency of the aortic valve a pulsus celer et altus is found the pulse climbs and falls quickly and has a large amplitude The terms water hammer [a toy] pulse (quick ascent) Corrigan pulse and collapsible pulse (quick descent) are often employed The pulse seems abrupt and jerky

These changes of the pulse stem from many factors At the time the ventricle ejects its contents the arteries are emptier than normal due to the regurgitation of blood in diastole and peripheral vasodilatation The velocity of arterial blood flow is increased and the pulse wave climbs steeply The period of isometric contraction is distinctly shortened as is the ejection time a large volume of blood is therefore discharged within a short time The peripheral arteries are widened The diastolic backflow of blood causes a steeper descent of the pulse wave while the large stroke volume makes the pulse wave higher

This pulse however is not pathognomonic since it may be present without insufficiency of the aortic valve and it may be absent despite a regurgitation Other conditions with a similar abnormal mechanism present a Corrigan pulse It may be pronounced in persistent patent ductus arteriosus and in arteriovenous fistulas In the latter instance such a pulse may appear even when a small peripheral artery e g the temporal artery communicates with the accompanying vein

Furthermore this pulse is rather common in hyperthyroidism and in mild as well as in the fully developed Graves disease but the mechanism is somewhat different Hypermotility of the heart and arteriolar dilatation are the contributing factors The water hammer pulse is also encountered in many infectious diseases with high fever of varying origin such as pneumonia with vasomotor paralysis Patients with atheromatosis and aortitis may present this pulse even when the aortic valve is normal in these cases the elasticity of the ascending aorta is diminished and the contents of the left ventricle are expelled immediately into the peripheral vessels This pulse is often pronounced in beriberi even in the mild occidental form since thiamine deficiency disturbs muscular metabolism and changes the tonus of the vascular tree The ventricles are hyperactive A collapsible pulse may also be seen in severe anemias

If these disturbances can be ruled out (and usually this is a fairly simple matter) one may infer the diagnosis and — with the exercise of due care — even the degree of the lesion from the celerity of the pulse In uncomplicated cases the celerity of the pulse is proportional of the degree of regurgitation

Pulsus celer may be absent despite marked valvular insufficiency when an advanced mitral stenosis coexists In this case the stroke volume is small since the left ventricle is not well filled Under these circumstances none of the peripheral signs of an aortic insufficiency need appear The auscultatory signs may also vanish if there is a marked mitral stenosis It is obvious that an accompanying aortic stenosis will also abolish the peripheral signs of an aortic insufficiency The character of the pulse in this combined lesion depends upon the predominance of one lesion or the other It is not rare for the peripheral vasoconstriction in hypertension and nephrosclerosis to abolish the Corrigan pulse of an aortic insufficiency Finally in a terminal stage myocardial weakness may abolish the pulse changes

Whenever the examiner suspects the presence of a Corrigan pulse the radial artery should be palpated with the patient s arm raised perpendicularly In this position the characteristics of a water hammer pulse are more pronounced than when the arm is horizontal not rarely the pulse seems normal unless the arm is elevated Hydrodynamic factors (the summation of the pulse wave with reflected waves) seem responsible for this difference (Wiggers) It is also advisable to palpate the carotid artery which may show alterations of the pulse at an earlier stage than the radial artery this is explained by the size of the carotid artery and its proximity to the heart

The radial as well as the carotid pulse should be palpated on both sides to determine whether or not differences exist Not uncommonly there is some discrepancy in the size of the radial pulse in normal subjects This discrepancy *might be anticipated since the course of the radial artery is subject to anatomic* variations On the other hand the existence of distinct changes when both brachial or carotid arteries are compared is an important sign of the syphilitic form of aortic insufficiency In vascular syphilis the ostia of the innominate subclavian or left carotid arteries are often narrowed or even completely occluded In such a case one brachial or carotid artery may show little or no pulsation These pulse differences although often attributed to an aneurysm are simply the consequences of the syphilitic process in the aorta and in many cases permit the differentiation of the two major forms of aortic insufficiency

CAPILLARY PULSE Some observers assign far too much importance to the so called capillary pulse in the diagnosis of aortic insufficiency Our feeling is that this sign has no value It may be encountered in normal individuals a fact known to Quincke many healthy people show it on hot days or when a hand is placed in hot water in order to dilate the peripheral arteries (Lewis) It is also found in other disorders e g mitral lesions arteriosclerosis and hyperthyroidism and is therefore not characteristic Even the term capillary pulse is improper in view of the fact that the phenomenon may be noted without pulsation of the capillaries themselves That the phenomenon of capillary *pulsation* seen with the unaided eye derives from a different mechanism than the type observed with the capillary microscope is a source of much confusion

Other Peripheral Signs The other oft mentioned peripheral signs of aortic insufficiency have just as little practical importance as the capillary pulse Traube s sound Duroziez s double murmur Musset s sign and other phenomena are found when the water hammer pulse is present Most of these signs may be elicited whenever there is a marked peripheral vasodilatation and they are found in the absence of aortic insufficiency as in beriberi and hyperthyroidism

Blood Pressure The blood pressure shows characteristic alterations The diastolic regurgitation of blood into the left ventricle diminishes the diastolic pressure which usually reaches a level below 50 mm Hg Sometimes the diastolic pressure cannot be measured at all since the sound over the vessel remains loud down to zero The pulse pressure or amplitude the difference between systolic and diastolic pressure is increased but it should be stressed that the diastolic blood pressure is often equally low in other conditions such as hyperthyroidism beriberi arteriovenous fistulas and persistent patency of the ductus arteriosus On the other hand the diastolic blood pressure may remain high if the regurgitation is accompanied by a marked stenosis of the aortic valve or hypertension with nephrosclerosis In the condition last named a diastolic blood pressure of over 100 mm Hg is not rare despite a pronounced aortic insufficiency

There is no characteristic change of the systolic blood pressure in this lesion It may be normal despite an advanced aortic insufficiency Occasionally however it may attain a remarkably high level in both the rheumatic as well as the syphilitic form In one case of rheumatic aortic insufficiency we observed a systolic blood pressure of 320 mm Hg The hypertension is attributed to rapid arterial filling under increased force during the short ventricular systole which ejects a larger stroke volume Owing to the increased diastolic filling systole is more forceful in accordance with Starling s law The loss of elasticity of the ascending aorta particularly in the syphilitic type of aortic insufficiency also contributes to the systolic hypertension

In aortic insufficiency as well as in other cardiac lesions the blood pressure may rise in the course of cardiac failure (stasis hypertension)

HILL S PHENOMENON In aortic incompetency the blood pressure in the lower extremities is markedly higher than in the brachial arteries sometimes by as much as 80 to 100 mm Hg This is called Hill s phenomenon The same situation is encountered although less frequently in such other conditions as hyperthyroidism and arteriosclerosis The difference in systolic pressure between the arms and legs in normal individuals usually does not surpass 40 mm Hg This sign has always been somewhat puzzling because such differences in pressure would not be anticipated in a system of communicating tubes Actually with the use of a direct method for the registration of blood pressure in the lower extremities in cases of aortic insufficiency much smaller differences between the arm and leg readings are found than indicated above The Hill phenomenon is probably due partly to the fact that a larger mass of tissues surrounding the arteries of the lower extremities must be compressed when the blood pressure is measured partly to the higher kinetic energy of the blood in the large vessels of

the legs (Bazett Gladstone) The arteries for the arms and head depart at a right angle from the aorta whereas the femoral artery is a direct continuation of the abdominal aorta Therefore the velocity head due to systole is much higher in the arteries of the legs The Hill phenomenon does not seem to have any practical significance It is also found in arteriovenous fistulas (Lewis and Drury)

Apical Impulse The apical impulse is often heaving owing to hypertrophy of the left ventricle Due to left ventricular dilatation the apex beat may be displaced downward The fact that a large stroke volume leaves the thoracic cage within a short time leads to increased negativity of intrathoracic pressure and causes retraction of the interspaces over the precordial area (Lang)

Percussion and Roentgen Examination

Corresponding with the various stages of decompensation cardiac shape may assume one of three patterns (1) the heart may be normal in size and shape (figure 23 a) (2) it may show an aortic configuration with varying degrees of left ventricular dilatation (figure 23 b) (3) it may assume the shape of a mitralized aortic heart (figure 23 c) Establishing the size and shape of the heart by means of percussion or x ray has great value because this permits an evaluation of the various compensatory mechanisms in operation and also yields important prognostic information

(1) As just stated the heart may be normal in size and shape Naturally such patients are rarely encountered in hospital wards but they are often seen in private practice especially when presumably healthy individuals are examined (life insurance athletes military service) A heart of normal size can be found not only at the beginning or with a slight insufficiency but also in fully developed lesions of long duration and associated with all typical palpatory and auscultatory signs

The abnormal dynamic mechanism in an aortic insufficiency consists of blood returning from the aorta into the left ventricle during diastole The left ventricular content increases to the extent of the volume of regurgitated blood Different opinions prevail concerning the volume In the highest estimates about 50 per cent of the stroke volume (30 ml) flows back into the left ventricle when the valves are completely incompetent The increase of the diastolic ventricular content by 30 ml alone is inadequate to produce a cardiac enlargement distinctly perceptible and recognizable as pathologic Considerably larger amounts of fluid must accumulate for a pericardial effusion to be demonstrated clinically A moderate slowing of the heart rate within normal limits prolongs diastole The increment thus added to the usual ventricular contents far surpasses that of aortic insufficiency Furthermore the left ventricle in these cases empties normally in systole and there is no increase of residual blood Therefore it is reasonable to conclude that no clinically demonstrable enlargement of the left ventricle need occur solely from the abnormal valvular mechanism in aortic insufficiency

A 72 year old physician was observed who had developed an insufficiency of the aortic valve following rheumatic fever at the age of six. The diagnosis was made by a competent internist and was frequently confirmed in the course of sixty six years. Nevertheless the heart was normal in size and shape when the patient was last seen.

(2) A healthy myocardium can perform the increased work demanded of it by aortic insufficiency without unduly disturbing the circulation. However with incomplete emptying of the ventricle greater amounts of residual blood and dilatation appear early if the myocardium is damaged. Dilatation of the left ventricle appears with a rapidity proportionate to the state of this structure. If the myocardium in general is healthy no visible enlargement of the heart need



FIG 23 Three orthodiagrams obtained from patients with aortic regurgitation (a) Heart of normal size and shape (b) the heart shows an aortic configuration with a widened aorta (c) the heart is mitralized

appear for years. Early enlargement takes place when the heart muscle is damaged by either the rheumatic or the syphilitic process (coronary stenosis). One may conclude therefore with justification that if marked dilatation occurs with considerable speed the myocardium is injured even in the absence of other signs. The state of the myocardium and not the extent of the valvular lesion determines the size of the heart. As a matter of fact enormous cardiac enlargement (cor bovinum) otherwise observed only in hypertension may be encountered in the late stages of aortic insufficiency. It is clear from this discussion that the rapidity with which the left ventricle enlarges in aortic insufficiency has definite prognostic significance.

Since the strain is on the outflow tract of the left ventricle in accordance with the rules discussed before the heart first becomes elongated and the apex beat is displaced downward. There is no widening of the heart. Later the apex becomes rounded the heart is somewhat more plump and with increasing dilatation of the left ventricle the waist of the heart becomes more pronounced leading to the typical aortic configuration (figure 23 b). The patient may be asymptomatic and normally active even when the enlargement of the left ventricle has reached a remarkable degree.

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tion of the aortic valve Whenever the diastolic murmur is heard best in this area the ascending aorta is markedly dilated and therefore moves near the chest wall The murmur is thus transmitted from the aortic valve to the second right intercostal space by the dilated aorta Conversely the more the murmur is transmitted toward the right shoulder the greater the aortic dilatation Since marked dilatation of the ascending aorta usually occurs in the syphilitic type the diastolic murmur of syphilitic aortic insufficiency is in most cases heard best over the second right intercostal space In the rheumatic form and especially when the aortic insufficiency is accompanied by a mitral lesion the murmur is heard best along the left lower sternal border as mentioned before Naturally there are exceptions to all rules no one should attempt to establish the etiology

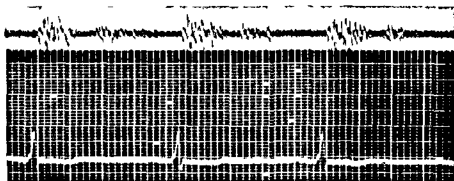


FIG 24 Rough systolic and high pitched diastolic murmur registered over the second right intercostal space near the sternum in a 54 year old man with syphilitic aortic regurgitation

of the lesion solely on the point of maximum intensity of the diastolic murmur In some cases of syphilitic aortic insufficiency the aorta does not dilate abnormally and the murmur is audible only at the lower sternal border Sometimes in rheumatic aortic lesions a combined insufficiency and stenosis of the valves causes the ascending aorta to enlarge markedly and the diastolic murmur to be heard best in the second right intercostal space Nevertheless in most cases the location of the diastolic murmur is a valuable aid in differentiating the two main types of aortic insufficiency

As previously mentioned the diastolic murmur may disappear in aortic insufficiency if accompanied by an advanced mitral stenosis or a tricuspid regurgitation

In rare cases (usually but not invariably in syphilitic aortic insufficiency) the diastolic murmur may be chirping mewing or cooing (sea gull murmur) This cooing like the sound of a cuckoo clock may be due to a tearing of the valve and actually appears not rarely in traumatic aortic insufficiency An explanation of this phenomenon may be retroversion of the right aortic valve toward the chamber (Bellet et al)

The systolic murmur which develops early in the syphilitic type of aortic regurgitation and which sometimes appears later in the rheumatic form may be very rough and harsh and may last throughout systole In other cases it is soft and distant When accompanied by a thrill it may be confused with the *murmur of aortic stenosis* *While aortic stenosis never occurs in the pure syphilitic* lesion it may be present when rheumatic and syphilitic changes in the valve are simultaneously present

The old conception that roughness of the aortic wall or valves is responsible for the murmur has been rightly relinquished Since the blood flows mainly in the center of the vessel mural friction scarcely comes into consideration as the cause of the systolic murmur The following explanation is probably more accurate Blood is forced from a dilated left ventricle into a dilated aorta through a ring of normal diameter This acts as a relative stenosis and the abnormal *turbulences and eddies create a murmur* *Actually* a similar murmur always develops over the aorta when the left ventricle and aorta are dilated (hypertension myocardial lesion heart block with bradycardia and an increased stroke volume) In aortic insufficiency the acceleration of the systolic blood flow due to greater filling of the left ventricle may participate in the development of the systolic murmur



FIG 25 Sketch to demonstrate the transmission of a systolic aortic murmur to the apex (hourglass murmur)

The point of maximum intensity of this systolic murmur is located at the classical site for *auscultation of the aortic valve that is* parasternally in the second right intercostal space If the murmur is sufficiently loud it is transmitted to the neck vessels All systolic aortic murmurs however have a second point of maximum intensity which is situated at the cardiac apex If the stethoscope is moved slowly from the second right intercostal space toward the cardiac apex the murmur becomes progressively softer over the right ventricle and then gradually grows louder as the apex is approached Apparently the murmur is transmitted to the apical area along the interventricular septum Systolic aortic murmurs are called hourglass murmurs since graphic representation of the two points of maximum intensity portrays the form of an hourglass (figure 25)

The presence of a loud systolic murmur over the apical area occasionally leads to the mistaken diagnosis of mitral insufficiency This diagnosis seems supported by the fact that the systolic murmur over the apex may sound entirely different from that over the aorta Nevertheless an alteration of the acoustic properties does not mean a different origin or mechanism of the murmur Murmurs may be filtered and modified by the transmitting tissues some vibrations are transmitted well some poorly while others are lost completely

Not rarely the upper point of maximum intensity disappears and no murmur is heard at the base while the loud systolic murmur persists over the apex This

is also wrongly interpreted as a mitral murmur The possibility of its transmission from the aorta is often forgotten This situation usually arises in patients with emphysema in whom the heart and ascending aorta are covered by lung At the apex where the left ventricle approaches the chest wall the murmur is audible Naturally in these cases the heart sounds disappear parasternally at the second right interspace

If the emphysema is more pronounced and the heart more thoroughly covered by lung cardiac auscultatory phenomena disappear even at the apical area in this instance heart sounds and murmurs are audible only over the lower end of the sternum near the xiphoid and often even more caudad

In an aortic insufficiency with marked dilatation of the left ventricle a relative mitral regurgitation often develops as described above The mitralization of the heart then progresses more rapidly a new systolic murmur appears over the apex and the second pulmonic sound becomes more accentuated

In some instances of rheumatic or syphilitic aortic insufficiency a tripartite murmur is heard between the apex and the lower end of the sternum It is composed of one systolic and two diastolic murmurs The reason for duplication of the diastolic murmur is unknown to us Both parts have the same intensity and seem practically identical The rhythm is like that found in gallop rhythm except that the sounds are replaced by murmurs

Austin Flint Murmur Occasionally in aortic insufficiency a presystolic or rumbling diastolic murmur is heard over the apex causing confusion with mitral stenosis This murmur the Austin Flint murmur is regarded by some as very common and is said to occur in 50 per cent of the cases We have found it to be uncommon Inexperienced physicians often confuse an impurity of the first or second heart sound with a murmur and make the diagnosis of mitral stenosis or Austin Flint murmur As a matter of fact it has been shown recently that a variety of acoustic phenomena may simulate the murmur of mitral stenosis in cases of aortic regurgitation (Luisada) With experience graphic registration is not necessary for differentiation

Many explanations have been advanced for the Austin Flint murmur Some believe that the diastolic influx of blood from the aorta causes the mitral valves to float if the floating leaflets are pushed close to the mitral orifice they may impede the atrial blood entering the ventricle Others think that the murmur is especially apt to occur in those cases of aortic insufficiency in which the aortic cusp of the mitral valve is forced back by blood regurgitating from the aorta this is said to hamper the inflow of blood from the atrium Another group believes that the murmur is created by the meeting of the two blood streams one from the left atrium and the other from the aorta

An unequivocal differentiation between this functional mitral stenosis the presumptive cause of the Austin Flint murmur and true mitral stenosis is possible only at necropsy

The character of the heart sounds lacks significance in the appraisal of the degree of aortic insufficiency Owing to left ventricular hypertrophy the first

heart sound at the apex may be very loud but it may also be submerged in or indistinguishable from the systolic murmur Likewise the second heart sound may be absent or faint in advanced cases as well as in early cases when the to and fro murmur is heard instead of the heart sounds Even with a well advanced aortic insufficiency the second sound may have a ringing tone We have seen one case in which two of the aortic leaflets were completely destroyed by bacterial endocarditis and only one half of the third leaflet functioned A very loud second aortic sound was heard until the end

The intensity of the second sound offers no assistance in the differential diagnosis between rheumatic fever and syphilitic aortic insufficiency

Occasionally when aortic insufficiency is severe and the water hammer pulse is pronounced a very loud sound is noted at the base of the heart with its greatest intensity in the supra and infraclavicular region It is usually confused with the first heart sound actually however it is not of cardiac origin Rather it is produced by systolic distention of the large arteries near the base of the heart and corresponds to the vascular sounds audible over the peripheral arteries in such cases

Rhythm The rhythm is usually regular atrial fibrillation is rather the exception

Rate The rate is often rapid This sinus tachycardia is prone to occur in young individuals rates of 120 per minute being not uncommon The tachycardia sometimes occasions the use of digitalis which is not indicated in a sinus tachycardia of this type The low mean arterial pressure in aortic insufficiency causes the tachycardia with the aid of a carotid sinus reflex The significance of this acceleration was recognized by Corrigan more than a century ago but thinking somewhat teleologically he regarded it a compensatory measure the tachycardia by shortening the duration of diastole reduces the amount of regurgitating blood

Electrocardiogram

In early uncomplicated cases the electrocardiogram shows only a left axis deviation more advanced cases present the pattern of left ventricular hypertrophy as in hypertension

Complications

With the exception of angina pectoris the most serious complication is subacute bacterial endocarditis If the patient with aortic regurgitation develops fever weakness loss of appetite and anemia this ominous complication should be suspected

Differential Diagnosis

While the diagnosis is easy in a fully developed pure aortic insufficiency it may be difficult when mitral or aortic stenosis coexists Earlier it was pointed out that all peripheral and auscultatory signs of an aortic insufficiency may disappear in such cases sometimes the correct diagnosis is possible only when

the results of the roentgen examination are correctly evaluated Thus a wide aortic knob showing strong pulsations may lead to the correct diagnosis of an unrecognized aortic insufficiency in the presence of a mitral lesion

A diastolic murmur at the same place and with the same characteristics is sometimes heard in mitral stenosis when a relative insufficiency of the pulmonary valve appears (Graham Steell murmur) The differentiation will be discussed later

Difficult occasionally is the differentiation from a patent ductus arteriosus or aneurysm of the sinus of Valsalva which has ruptured into a ventricular cavity The condition of patients with the latter condition rapidly deteriorates and death soon follows Usually in both of the above mentioned conditions there is a continuous murmur with systolic accentuation A systolic murmur followed by a diastolic one over the pulmonary artery appears in patients with atrial septal defects

Diastolic murmurs in the same area as those of aortic insufficiency are sometimes heard in hyperthyroidism In such patients the differentiation may be difficult since both conditions produce the same peripheral signs

In a cardiac aneurysm a soft high pitched diastolic murmur is sometimes audible to the left of the sternum, this murmur may be confused with the murmur of aortic insufficiency until necropsy reveals the correct diagnosis (Scherf and Brooks) Peripheral signs of aortic regurgitation are absent

The most important problem in the differential diagnosis is the distinction between the rheumatic and syphilitic type of aortic insufficiency Very often the history throws no light on the situation In many cases a history of syphilis cannot be obtained for a variety of reasons The serologic tests are not decisive for up to 15 per cent of patients with luetic aortic insufficiency have an entirely negative serology About 40 per cent of the rheumatic cases are unaware of a previous attack of rheumatic fever

Two points mentioned during the discussion of symptoms and signs may be of value

(1) The presence of a marked difference in the strength of the brachial or carotid pulse between the two sides is a strong argument in favor of a syphilitic aortic insufficiency

(2) If the murmur is heard best over the second right intercostal space and particularly toward the right shoulder pronounced dilatation of the ascending aorta and therefore syphilitic aortic insufficiency should be suspected

Undoubtedly in a certain number of patients the differential diagnosis is impossible

Prognosis

As pointed out earlier the prognosis depends mainly on the status of the heart muscle Since myocardial damage during rheumatic fever is rarely very pronounced the outlook for patients with a rheumatic aortic insufficiency usually is rather good The frequent concurrence of coronary orifice stenosis in the syphilitic form necessitates a more guarded prognosis While some statistics suggest

that the average duration of life from the beginning of symptoms may approximate two years in syphilitic aortic insufficiency the process may come to a standstill at any time and complete compensation for 15 or more years occurs Nevertheless the prognosis is certainly more serious than in the rheumatic type

Surgery

Surgical therapy of aortic regurgitation is only in its infancy and further developments may be expected (Hufnagel)

The Hufnagel plastic (lucite) valve leads to hemolytic anemia because of the mechanical destruction of red cells

A traumatic aortic insufficiency was found in a 17 year old man who had been kicked in the chest by a horse and became unconscious A plastic aortic valve was inserted and the patient was symptom free and working 14 months after the operation (Leonard et al)

STENOSIS OF THE AORTIC VALVE

Incidence

Stenosis of the aortic valve (aortic stenosis) is a common valvular lesion This fact must be stressed because it contradicts the opinion which prevailed widely until a few years ago To be sure the diagnosis often is made only when the lesion is rather advanced the diagnosis of a moderate stenosis may be difficult The lesion is more common in men than in women the ratio being 3 to 1 (Kumpe and Bean)

Etiology

Rheumatic Fever In a majority of cases aortic stenosis results from rheumatic fever causing endocarditis in which the aortic valves fuse usually an insufficiency accompanies a stenosis Rheumatic aortic stenosis without insufficiency is very rare but the latter is often not diagnosed because of the absence of peripheral signs and murmurs

Atherosclerosis The occurence of another form of aortic stenosis the atherosclerotic type is established but its frequency is at present not fully determined Karsner thinks that rheumatic fever is responsible for the majority of advanced aortic stenoses while others maintain that atherosclerosis is responsible in most instances The atherosclerotic process begins at the base of the valve in the sinus pocket and slowly advances to the free edge that is in a direction opposite to that occurring in rheumatic fever Since many patients with rheumatic aortic stenosis live to an old age since lime salts are commonly deposited in the valves following rheumatic verrucous endocarditis and since a positive history of rheumatic fever may be absent in rheumatic aortic stenosis an atherosclerotic aortic stenosis is frequently diagnosed in patients with rheumatic valvular disease This mistake is understandable in view of the fact that as emphasized in the original description of atherosclerotic aortic stenosis the ascending aorta in these cases need not show evidence of atherosclerosis

Congenital Congenital stenosis of the aortic orifice due to a malformation is not rare It may involve the conus of the left ventricle the aortic orifice itself or the supravalvular aorta

As mentioned above syphilis never causes aortic stenosis The presence of syphilitic aortitis or regurgitation therefore precludes the existence of an aortic stenosis unless an additional rheumatic valvulitis exists

Mechanism

Stenosis of the aortic valve is easily compensated As in hypertension the augmented resistance increases the residual blood the diastolic filling and thus the initial stretch of the fibers of the left ventricle This causes increased energy of contraction and hypertrophy Since the stenosis progresses gradually there is ample time for these changes to develop The hypertrophy may assume great dimensions in aortic stenosis Animal experiments have shown that the aortic orifice must be reduced to less than one quarter its normal size before the output diminishes and changes of blood pressure and pulse appear (de Heer) Even under physiologic conditions the valves approximate rather closely during a great part of systole and permit only a small opening The normal aortic orifice is about 2 0 square centimeters in area In confirmation of the experimental findings Gorlin et al found that an aortic orifice of 0 5 cm is critical since it makes necessary a high intraventricular pressure (up to 200 mm Hg) The isometric contraction period like the ejection period is slightly prolonged

Symptoms

The adjustment of the circulation to the lesion is usually so complete that patients with extreme aortic stenosis may pursue athletic activities and may undertake arduous physical strain without symptoms Naturally here as in other valvular lesions a healthy myocardium is the necessary prerequisite

The excellent compensation of aortic stenosis makes it understandable why patients are sometimes encountered who had an aortic stenosis since early childhood the first symptoms of which appeared only when they were 60 years old or later Patients may even be over 70 when the first evidence of left ventricular failure due to aortic stenosis appears Cheyne Stokes respiration and paroxysmal nocturnal dyspnea are the first signs of decompensation

Some patients however develop symptoms very early in the disease at a time when full compensation prevails They complain of fainting and anginal pain

Syncope Attacks of syncope and loss of consciousness may follow brisk movements and sudden change of posture or overexertion (Gravier Callavardin) Often they appear without any visible reason Even epileptiform convulsions occur causing these patients to be treated for epilepsy until the real reason for the attacks is discovered Contrary to frequent statements such attacks also occur at rest and even during sleep

The attacks are not rare for syncope was noted in 31 of 235 cases of aortic stenosis (McGinn and White) Hammarsten found syncope in 16 of 63 subjects

with aortic stenosis Unconsciousness may last from a few minutes to a half hour The convulsions are not as a rule generalized Few studies of the pulse rate facial color or blood pressure during the attacks are available since the episodes recur too infrequently to permit observations and records Marked arrhythmias were found in electrocardiograms taken during an attack of syncope it seems however that the syncope appears before the arrhythmia The latter is not marked enough to cause unconsciousness

The mechanism of these attacks is not satisfactorily explained A cerebral ischemia is probable but unproven the long duration of some episodes however makes a profound cerebral ischemia dubious There are no sequelae recovery is prompt and complete This and the absence of aura help in the differentiation from epilepsy It has been suggested that the syncope of aortic stenosis might be due to some disturbed carotid sinus reflex mechanism Pressure on the carotid sinus of such patients however does not initiate an attack and the responses are not abnormal Nevertheless it is conceivable that the carotid sinus in these patients responds abnormally to physiologic stimuli such as a sudden fall of blood pressure consequent to dilatation of the splanchnic vessels Thus regulation of the blood pressure level is disturbed

Anginal Pain This is another typical complaint Kumpe and Bean noted cardiac pain in 37 per cent of their cases The pain often radiates in the usual manner to the left arm and appears on exertion or excitement like the classic angina on effort In addition it often awakens the patient from deep sleep Its mechanism will be discussed later in the chapter on angina pectoris

Signs

Pulse In advanced cases the pulse shows definite changes the exact opposite to the pulsus celer et altus of aortic regurgitation It is called pulsus parvus because of its small size in button hole aortic stenosis even the carotid pulse is scarcely palpable It is also called pulsus tardus because of its slow rise The pulse is often anacrotic While the blood pressure is often low we have frequently found normal values and hypertension is not less common than in the average population The auscultatory gap (see chapter on hypertension) is usually found during the auscultatory measurement of the blood pressure

Palpation A heaving apex beat may be felt since the left ventricle is hypertrophic This sign however is often missed In most cases a systolic thrill is palpable over the aortic area in the second right interspace and also over the carotid vessels particularly on the right side It is common because of the low pitch of the murmur in aortic stenosis Sometimes it can be palpated only in deep expiration and when the patient sitting or standing bends forward slightly It is absent with pulmonary emphysema A similar thrill however may be present whenever a rough systolic murmur arises at the same place therefore it may occasionally be noted in atheromatosis and syphilitic aortitis The systolic thrill is also found over the apex and may be located exclusively there when emphysema prevents its palpation over the aorta

Percussion and Roentgen Examination Both methods often fail to reveal any enlargement of the left ventricle for many years even when the lesion is advanced This is explained by the fact that the primary change is hypertrophy which starts at the outflow tract of the left ventricle Dilatation which may not appear until late proceeds along the axis of the left ventricle displacing the apex beat downward This displacement is often missed during the examination when the apex beat is not felt and the cardiac shadow merges with the abdominal shadow Enlargement of the heart along the transverse diameter causing the aortic configuration is a late event

On x ray examination but rarely on percussion an unusual widening of the aorta is found involving the initial portion of the ascending aorta This finding is surprising since the small pulse and slow ejection of blood might lead one to expect the aorta to be less dilated than it is for instance in aortic insufficiency If one has the opportunity to examine at necropsy a patient whose aorta seems to have been markedly dilated during life every sign of dilatation may be absent This suggests that the dilatation is dynamic Due to the great force with which the blood is ejected through the stenotic valve by the hypertrophied left ventricle a jet action is present and dilatation of the aortic wall is produced In two cases of aortic stenosis with superimposed subacute bacterial endocarditis we found an endarteritis at autopsy Vegetations were implanted in the aortic wall just where one would assume that the blood coming from the left ventricle struck the side of the vessel and caused a lesion of the endothelium Schnoor et al expressed the opinion that turbulences and repetitive pulsatile stresses cause a structural fatigue and dilatation

Careful fluoroscopy reveals calcification of the aortic valves in many cases This finding greatly supports the diagnosis Pyke and Symens who examined radiologically 400 males over 60 years of age found calcifications of the mitral valve in 2 75 per cent and of the aortic valves in 3 5 per cent It is necessary to differentiate valvular calcifications from those in the pericardium and myocardium (following necrosis in myocardial infarction) and calcium deposits in old mural thrombi Calcification occurs rather often in elderly subjects in the annulus fibrosus of the valve (the cardiac skeleton) (figure 26)

Sosman recommended certain rules that should enable one to distinguish between mitral and aortic valve calcifications The former are situated more toward the apex in the antero posterior picture in the left anterior oblique position when the heart just clears the spine the mitral valves are in the posterior third of the cardiac shadow while the aortic valves are in the middle third Valvular calcifications are C or J shaped and linear or diffuse

Auscultation A rough systolic murmur is usually found over the second right intercostal space This murmur radiates to the neck vessels and also to the apical area It sounds very close to the ear is prolonged and may fill all systole In some cases it is short and resembles the murmur heard in atheromatosis or aortitis Kumpe and Bean found it in only 83 per cent of proved cases In phonocardiograms one finds that the vibrations gradually increase in size and after

reaching a maximum height decrease (diamond shaped murmur) Figure 27 shows this murmur registered over the second right intercostal space in a 32 year old patient with aortic stenosis Similar murmurs are found in pulmonary stenosis and some congenital heart lesions



FIG 26 Atheroma of the aorta with calcium deposits in the arch and calcification of *the heart skeleton*

Quite characteristically either the systolic murmur of aortic stenosis is not followed by a second sound or else the second sound is distant This is understandable if one recalls how the valves are transformed into a firm calcified ring in which the individual cusps are no longer discernable closure of these valves at the end of systole therefore is impossible However the second pulmonic sound may be heard over the second right intercostal space A normal second aortic sound is heard in patients with an infravalvular congenital aortic stenosis In

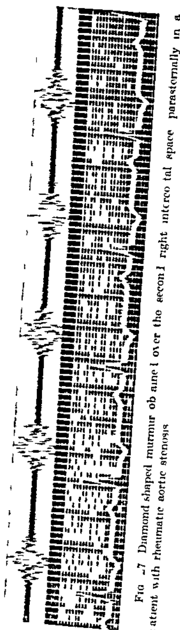


Fig. 27. Diamond shaped murmur obtained over the second right intercostal space parasternally in a patient with rheumatic aortic stenosis

Fig. 28. The systolic diamond shaped murmur in a patient with aortic stenosis is louder the longer the preceding diastole

such cases the systolic murmur may be heard only over the left second or third intercostal space to the left of the sternum The loud systolic aortic murmur becomes distinctly softer when the strength of the left ventricle diminishes and louder when the condition of such a heart is improved by digitalis We have seen button hole stenoses of the aortic valves become silent with heart failure In such cases no sounds or murmurs are audible over the aorta Its loudness depends on the diastolic filling of the left ventricle (figure 28) The peripheral arteries scarcely pulsate but the patient may be able to walk without dyspnea and he can lie flat in bed without orthopnea

A diastolic murmur of aortic regurgitation — if present — supports the diagnosis It is inaudible in about 50 per cent of the cases When present it is heard usually at the lower left sternal border Being often very faint it is easily missed

A systolic apical murmur is always present Usually it is a transmitted aortic murmur but in advanced stages of dilatation of the left ventricle it may be caused by a relative mitral insufficiency

Arrhythmias are rare An unexplained bradycardia is as common as the tachycardia of aortic regurgitation This is fortunate because the prolongation of diastole (and partly also of systole) is advantageous in the presence of an aortic stenosis This bradycardia however is often deceptive and may dissuade the *physician from giving digitalis if necessary*

A systolic click (claquement aortique protosystolique) appearing 0 06 to 0 08 second after the onset of the first heart sound has been described

Electrocardiogram In late stages the electrocardiogram shows evidence of left ventricular hypertrophy Because of the elongation of the heart (egg shaped) and due to the dilatation of the outflow tract only left axis deviation is often missing and only inverted T waves appear in the standard leads

Differential Diagnosis

If there is a characteristic pulsus tardus a systolic thrill and a loud prolonged systolic murmur over the aorta and the second aortic sound is absent the diagnosis of aortic stenosis is easy This is particularly true if the heart shows the anticipated configuration and the patient complains of fainting spells and anginal pain

The diagnosis and differentiation from other conditions will be difficult if the lesion is less advanced Sometimes it will be impossible to decide whether a rheumatic aortic insufficiency with a slight stenosis of the valves exists or whether we are dealing with a pure aortic insufficiency In syphilitic aortic insufficiency the systolic aortic murmur may be very loud and a thrill may even be palpable over the aorta In the average case of syphilitic aortitis however the second aortic sound is loud in elderly people with emphysema on the other hand the second aortic sound may become inaudible in a normal heart and this makes differentiation difficult

When there is no evidence of aortic regurgitation the differentiation between an aortic stenosis and atheromatosis or aortitis may be difficult It is not unusual to suspect atheromatosis in a patient of 70 years or more and to find an aortic stenosis of rheumatic origin at necropsy In this case as well the presence or absence of an accentuated second aortic sound within certain limits may help in the differentiation

An aortic stenosis may also be overlooked if it occurs in a patient with an advanced mitral stenosis for the mitral lesion may dominate the clinical picture

Catheterization Confirmation of the diagnosis by catheterization of the left ventricle although possible is not without risk and therefore is better omitted The catheter must be introduced via a peripheral artery Its introduction into the left ventricle may be difficult It may obstruct completely the very small lumen of the aortic orifice A very high systolic blood pressure in the left ventricle with a much lower one in the aorta is characteristic

Prognosis

The excellent prognosis of the lesion and the long duration of full compensation has often been stressed Many patients with aortic stenosis live active lives without ever knowing that they have any heart disease The average age reached by patients with pure aortic stenosis is 65 years (Mitchell et al) This includes of course patients who developed the lesion late in life because of atherosclerosis Grant alone comes to a different conclusion and calls the prognosis of aortic stenosis least favorable

Patients with aortic stenosis may die suddenly This event was noted in 6 of 28 observations (Cabot) and it occured in 9 of 11 cases in another group (Marvin and Sullivan) It seems probable that the sudden death is in some way associated with the attacks of loss of consciousness or the anginal pain due to myocardial ischemia The latter may induce ventricular fibrillation

Surgery

Surgical therapy of aortic stenosis with the finger fracture method was recommended as early as 1913 (Tuffier) The operation has been revived in recent years and with progress in surgical technic it may bring success Because of the frequency of calcification of the valves surgery cannot always yield a good result In view of the good prognosis of most cases the operation should be reserved for those patients with progressive stenosis of the aortic valves in which anginal pain syncope or failure of the left ventricle make the outlook without surgery rather dubious The approach from the ventricle is difficult as compared to pulmonary stenosis where it is employed with success This depends upon the great thickness of the left ventricle and the very high pressure within it According to one proposal a dilator should be introduced from the apical area of the left ventricle The mortality is still near 16 per cent but diminishes gradually as better technics are developed A transaortic approach at present seems to provide better

results and a lower mortality Baker and Campbell had 6 deaths in 16 operated patients good results were obtained only in five The greatest danger is creation of an aortic regurgitation Personal experience taught us that in dog experiments with the heart exposed in situ creation of such a lesion during an attempt at severing the left bundle branch leads to an immediate tremendous dilatation of the left ventricle and cardiac standstill

MITRAL STENOSIS

Mitral stenosis one of the most common valvular lesions is often combined with mitral insufficiency Observations during surgery reveal however that not rarely the stenosis is pure For didactic reasons only the latter type of mitral stenosis will be considered here

Etiology

Apart from very rare congenital malformations which cause atresia or narrowing of the mitral orifice traumatic mitral stenosis and rare instances of a healed bacterial endocarditis the etiology of the lesion is always rheumatic fever A previous history of rheumatic fever to be sure cannot be obtained in about 40 per cent of the cases These patients deny having had joint manifestations chorea or tonsillitis and even report that they have never suffered from a febrile disease

Two forms of congenital mitral stenosis exist A child may be born with a rheumatic mitral stenosis In such cases we may assume that the mother had rheumatic fever during pregnancy In the other type actual malformation of the mitral valves exists and defects of the atrial septum coarctation and aortic stenosis usually are also present (Ferencz et al)

Age Sex Owing to the relationship to rheumatic fever the maximum incidence of mitral valve disease is between the ages of 10 and 40 although many cases are observed in younger or older individuals Mitral stenosis was treated successfully by surgery in a child three years old Females seem more prone to develop rheumatic mitral disease this is especially true for mitral stenosis

Pathology

The rheumatic process discussed in a previous chapter leads to fusion of the mitral leaflets with thickening and secondary calcification in an appreciable number of cases This process usually accompanied by shortening and fusion of the chordae tendineae may be only just discernible or very severe In an advanced case of mitral stenosis the orifice is so narrowed and distorted that it is compared according to its shape with a button hole or fish mouth If the shortening of the chordae tendineae displaces the orifice toward the apex a funnel form of the mitral orifice is found at postmortem examination Sometimes an extensive calcification may involve the entire ring

Pathophysiology

Dynamic changes appear only in a rather advanced experimental stenosis since slight alterations are easily overcome by compensatory mechanisms In experimental mitral stenosis reduction of the mitral orifice to one quarter of its natural size is necessary before the resistance becomes so high that the rise of pressure in the left atrium is unable to compensate for it A valvular area of 1 square cm is critical since a pressure head to guarantee a normal cardiac output is necessary that is greater than the osmotic pressure of the plasma proteins Blood pressures of 160 mm Hg have been measured in the pulmonary artery with an intracardiac catheter That is 8 times the normal pressure A hydraulic formula has been given which permits one to calculate the area of the mitral valve orifice in diastole The rise of pressure within the left atrium leads to hypertrophy and later to dilatation of this chamber The pressure within the lesser circuit also rises early and increases the strain on the right heart Filling of the left ventricle decreases and leads to an atrophy which involves mainly its inflow tract

The volume of intrathoracic blood rises but slightly as opposed to left ventricular failure where it is markedly increased The progressive vascular changes in the lesser circuit in mitral stenosis are responsible for this There is at first a marked functional narrowing the cause of which is local anoxia (see Cor pulmonale) later organic changes of the vessels occur (see below) Pulmonary and bronchial arteries anastomose with each other and the pulmonary veins are overloaded The bronchial arteries show a marked hypertrophy of the media The pressure in the pulmonary capillaries and in the left atrium is estimated by pushing the tip of a catheter into a small pulmonary artery

The lesion develops slowly and its evolution requires at least six months and often longer before it can be recognized

Symptoms

The patient may have few complaints Not rarely mitral stenosis is found accidentally and the patient denies any symptoms relating to the lesion This situation occurs more frequently than in aortic insufficiency but such cases are known to every physician Careful interrogation may reveal that the capacity for exertion has always been somewhat reduced and rapid climbing of stairs or walking uphill has provoked dyspnea and palpitation Since however similar symptoms may appear in the absence of valvular lesions in healthy people especially in the obese and since the symptoms remained stationary the patient never consulted a physician nor complained of his condition Once in a while the physician sees such patients who have had mitral stenosis for at least 30 to 40 years come for a routine physical examination and assert they feel absolutely normal Occasionally a woman who has had a mitral stenosis since childhood seeks medical advice for the first time during or after the menopause when cardiac complaints typical for the climacteric develop At other times mitral stenosis is discovered during pregnancy or when a subacute bacterial endocarditis develops

Dyspnea In the majority of cases in contrast to the lesions of the aortic valve symptoms appear early While the left ventricle can maintain compensation for a long time in an aortic lesion in mitral stenosis the burden of compensation falls upon the left atrium The latter is equal to this task only in the presence of a very slight stenosis Even when the left atrium is able to force sufficient blood through the narrowed orifice at rest this becomes impossible when the demands are increased by physical exertion Stasis in the left atrium and engorgement in the lesser circuit appear with shortness of breath at first only upon severe exertion but later even on minimal activity In some cases the lungs become engorged so quickly on exertion excitement or the increase of rate that severe attacks of pulmonary edema appear Dyspnea may be so severe that any physical effort is difficult and the patient is forced to remain in a sitting position due to orthopnea

Patients with mitral stenosis do not have cardiac asthma or Cheyne Stokes respiration unless complications exist which lead to left ventricular failure Pulmonary edema is not too rare but it is a special type which has been discussed in the appropriate chapter

In recent literature the statement is often encountered that paroxysmal nocturnal dyspnea occurs in patients with pure mitral stenosis If one interprets this phrase to mean dyspnea appearing suddenly at night it is correct An exciting dream or sexual intercourse may cause dyspnea at night or the patient may slide down from his pillows and become dyspneic If by the term paroxysmal nocturnal dyspnea one understands the well defined forms of dyspnea discussed in the first chapter of the present volume then it must be said that patients with mitral stenosis are singularly free from this form of dyspnea It has never become clear to us why mitral stenosis with the marked reduction of cardiac output does not show the several forms of paroxysmal dyspnea such as cardiac asthma and Cheyne Stokes respiration

For obvious reasons digitalis is useless for the treatment of pulmonary edema in mitral stenosis The use of mercurial diuretics and morphine — given prophylactically — in minute amounts (15 to 20 drops of a 1 per cent solution of morphine hydrochloride in water or a 50 mg tablet of Demerol prior to sexual intercourse) may prevent the attack

Palpitation This symptom appears in the early stages It is noted more frequently at night and awakens the patient No satisfactory explanation for this phenomenon is known and the reason for its frequent occurrence in mitral stenosis are equally obscure The quick systole due to incomplete filling of the left ventricle may contribute to the sensation of palpitation

In hyperthyroidism and in cardiac neuroses palpitation may be due to increased rate and hypermotility of the heart The rate alone however does not seem to be a decisive factor in evoking this symptom for palpitation may be absent in a paroxysmal tachycardia when the rate is over 250 and it may also be absent despite marked pounding of the chest wall by cardiac pulsations

It is not rare in bradycardia in this instance it is due perhaps to the increased filling of the heart during prolonged diastole

Fatigue In advanced mitral stenosis fatigue is often an outstanding symptom The marked reduction of cardiac output is presumably responsible The cardiac output per minute may fall to 2 liters

Anginal Pain A small percentage of patients with mitral stenosis complain of anginal pain which often appears at rest and occasionally is not relieved by nitroglycerin Stuckey found pain in 8 5 per cent of 400 patients with mitral stenosis Scherf and Goldhammer found a positive electrocardiographic exercise test in such patients proving that cardiac hypoxia was responsible in the patients examined Compression of the left coronary artery between the left atrium and pulmonary artery or displacement and compression of the left coronary orifice by scars in the mitral valves have been proferred as explanations but they lack satisfactory proof The intermittent claudication occasionally observed in mitral stenosis in the absence of peripheral vascular disease shows that a diminished minute volume may be responsible

Signs

Complexion Sometimes inspection reveals the typical mitral facies with the malar flush and cyanotic tint of the lips and ear lobes Often however patients look normal Cyanosis in mitral stenosis is caused by pulmonary congestion by pulmonary vascular sclerosis in later stages or by increased peripheral utilization of the blood oxygen and stagnation in the advanced stage with right heart failure

Therefore cyanosis may be absent early unless pulmonary congestion is present It may diminish or disappear after having been present if the liver enlarges moderately and venous congestion develops due to right heart failure

Pulse Palpation of the pulse has considerable importance in the appraisal of this valvular lesion In advanced mitral stenosis filling of the left ventricle in diastole becomes so reduced that the stroke volume is diminished and the pulse is very small it may be scarcely palpable at the wrist even if it is felt in the larger carotid arteries If the patient has only a slight stenosis of the valve the pulse is normal One may infer therefore to a certain degree the amount of stenosis from the amplitude of the pulse In a beginning stenosis the pulse is normal but it becomes smaller as the stenosis increases Other physical signs are less informative in regard to the degree of stenosis than the pulse Thus murmurs may be both absent when the stenosis is advanced and very loud in the initial phase of the disease

Mitral stenosis and mitral insufficiency are often combined Under these circumstances the pulse alone reveals which lesion predominates As will be noted later mitral regurgitation does not decrease the size of the pulse Therefore if the pulse is normal in a combined mitral lesion it may be assumed that the stenosis is not extreme A small pulse in such cases indicates an advanced stenosis

even when the murmur of stenosis is absent and the murmur of mitral insufficiency is very loud

The pulse is also poorly filled and small in stenosis of the aortic valves in myocardial weakness and in the shock syndrome but the differentiation usually is easy

Blood Pressure In a youthful patient with mitral stenosis the blood pressure tends to be lower than the average level for the same age in the general population With increasing age (or with the appearance of decompensation) the blood pressure often rises and sometimes reaches a high level Some believe that the incidence of hypertension in mitral stenosis is the same as in the general population

Palpation Examination of the thorax and especially of the precordium by palpation in mitral stenosis yields so many signs that this method of investigation permits the diagnosis in most cases The apical impulse often remains at its normal site This might be anticipated since the left ventricle does not assume the burden of compensation and does not enlarge The right ventricle dilates only at a later stage and at this time the apex beat may be felt lateral to but never below its normal location If the apex beat is displaced downward the left ventricle is dilated and some complication such as mitral or aortic insufficiency exists and has produced the left ventricular enlargement

The apical impulse is abnormal in another respect It becomes snappy and quicker than normal In a normal heart if the apex can be felt at all it gives the impression of a slow pulsation In left ventricular hypertrophy it is heaving and particularly slow In a mitral stenosis however it is very short This alteration of the apex beat corresponds to the accentuation of the first heart sound a very common finding in mitral stenosis and enables one to make the correct diagnosis in the numerous instances when murmurs are absent

In an advanced mitral stenosis the left ventricle is smaller than normal sometimes it is even atrophic While it normally constitutes the most massive section of the heart in advanced mitral stenosis the left ventricle often looks like an appendage to the rest of the organ The left atrium right atrium and right ventricle hypertrophy and dilate in the evolution of the lesion but the left ventricle does not participate in the compensation The atrophy is usually attributed to the inadequate filling of the left ventricle and the fact that it involves the inflow tract primarily suggests that this assumption is correct

Another reason for the atrophy of the left ventricle also deserves consideration During the last years of life patients with advanced mitral stenosis are compelled to avoid the least exertion because this provokes dyspnea Such enforced inactivity which results in considerable atrophy of the skeletal musculature attains very striking proportions in mitral stenosis There is a strict parallelism between the status of the skeletal muscles and the state of the left ventricle In muscular athletes the left ventricle is stronger and heavier than in the average person in sedentary individuals who are physically inactive the left ventricle is weaker and less capable of performance Probably part of the left ventricular atrophy in cases of advanced mitral stenosis is due to inactivity of the patient

This fact should make one hesitate to limit the activity too strictly in patients with valvular lesions *All* physical exertion should not be forbidden The patient should be permitted to do as much physical work (initially under supervision) as he can without symptoms Like every other muscle the heart must also do its share of work in order to retain as much functional capacity as possible

A diastolic thrill is often palpable in the apical area A diastolic thrill means a diastolic murmur the significance of this lies in the fact that diastolic murmurs are found only in organic heart disease Systolic thrills which accompany systolic murmurs occasionally may be devoid of significance when the murmur is functional or physiologic The thrill of mitral stenosis appears more often if the apical area is palpated with the patient lying on his left side Its diastolic character is easily determined when the carotid pulse is palpated simultaneously and it is found that one does not coincide with the other

The regularity with which the murmur of mitral stenosis is accompanied by a thrill is explained by the fact that the murmur is low in pitch and the chest is resonant to low pitched murmurs Vocal fremitus is scarcely palpable in individuals with high pitched voices (mostly women) while it may be very distinct in men with deep voices (chest voice) This accounts for the usual absence of thrills in insufficiency of the aortic valve with its soft high pitched murmur The murmurs in all stenotic mechanisms of organic heart disease are low pitched and cause thrills This is also exemplified by the murmurs in aortic stenosis and in congenital cardiovascular defects

Occasionally the murmurs are so low pitched and have such coarse vibrations of large amplitude that they can be better palpated than heard The human ear is unable to perceive murmurs with less than sixteen vibrations per second Thus it occasionally happens that a patient with mitral stenosis presents a distinct thrill yet the murmur is very short or even inaudible

Palpation also reveals the signs of right ventricular hypertrophy that is a diffuse pulsation over the entire precordium Since the outflow tract of the right ventricle bears the chief burden of compensation and the conus of the right ventricle projects as the most ventral part of the heart systolic pulsation in the conus area may be pronounced Furthermore a brief but distinct impact is often felt in the conus area along the left cardiac border This impact follows the slow systolic pulsation over the precordial area and does not coincide with the carotid pulse It corresponds to the closure of the pulmonic valve which produces the second pulmonic sound The second pulmonic sound is normally palpable over the area of the pulmonary conus only in early childhood In adults palpability of the pulmonic sound is just as significant as the marked accentuation that always accompanies it Occasionally the closure of the pulmonic valve is palpable only during expiration

The wealth of manifestations on palpation — the snappy apical impulse the diastolic thrill at the apex the diffuse pulsation over the precordium and the more circumscribed systolic movement over the conus area of the right ventricle the distinctly palpable closure of the pulmonic valve — all these signs permit

the immediate diagnosis of mitral stenosis in a majority of cases By palpation of the pulse one can determine the extent of the lesion

To be sure even moderate emphysema makes the detection of these phenomena difficult or impossible Moreover some of the above mentioned phenomena occur in the absence of mitral stenosis Thus in the hyperactive heart of hyperthyroidism and of many patients with cardiac neuroses in some cases of beriberi or hypertension a diffuse precordial pulsation may be found in the absence of right ventricular hypertrophy In hyperthyroidism and cardiac neurosis the apex beat may be snappy and even preceded by a very short thrill By considering the other physical findings however a differentiation is usually easy

Percussion and Roentgen Examination

The size and shape of the heart in mitral stenosis may reveal three different situations which like the three cardiac contours seen in aortic insufficiency correspond to three sequential stages of the lesion Such findings are (1) a heart of normal size and shape (2) a mitralized heart of normal size (3) an enlarged mitral heart

(1) *For many years in cases of mitral stenosis the heart may* be perfectly normal in size and shape despite the presence of a loud presystolic murmur For obvious reasons this event is rare in clinics and in hospital wards but it is not uncommon in private practice One of us collected within one year 16 cases of mitral stenosis which did not present changes in the contour or size of the heart This situation prevails as long as the left atrium by hypertrophy alone is able to force sufficient blood into the left ventricle Under these circumstances no stasis develops no visible enlargement of the left atrium appears and the cardiac shape is normal Left atrial hypertrophy cannot be percussed and is not visualized by x ray *examination Sometimes the heart retains its normal shape* even if the auscultatory and roentgenologic findings indicate some congestion in the lesser circuit and the right ventricle becomes hypertrophic Therefore mitral stenosis should not be excluded in doubtful cases on the basis of normal x ray findings The heart may be normal in size even with the presence of a tight mitral lesion

(2) When left atrial hypertrophy no longer successfully maintains compensation increasingly larger residues of blood remain in the left atrium at the end of systole and dilatation develops The elevated pressure in the left atrium leads to a similar increase *within the pulmonary veins and soon—in a manner not completely* clear — in the arterial segment of the lesser circulation The elastic wall of the pulmonary artery expands The increased work for the right ventricle leads to a hypertrophy and dilatation of the outflow tract the conus area

The dilatation of the outflow tract of the right ventricle as pointed out before develops cephalad This change occasionally combined with dilatation of the left atrium causes the normal waistline on the left cardiac border to disappear and mitral configuration is found (figure 29 a)

A third mechanism is considered an important factor in the disappearance of the cardiac waist particularly in the late stages of mitral stenosis Dilatation of the right ventricle causes the heart to rotate around its axis to the left This rotation around the cardiac axis is clockwise (if the examiner stands opposite the patient) and is due mainly to an enlargement of the outflow tract of the right ventricle which lying anteriorly with an almost perpendicular axis fills the waistline if it becomes dilated Enlargement of the inflow tract counteracts this rotation and may even nullify it In a similar manner the heart rotates to

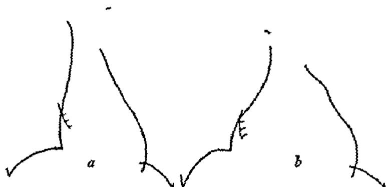


Fig. 29 Two orthodiagrams obtained from patients with mitral stenosis (a) Mitral configuration with moderate dilatation in the transverse diameter (b) Marked dilatation of the heart to the right and left In both instances the left atrium is visible on the right side

the right (counter clockwise) with dilatation of the outflow tract of the left ventricle dilatation of the inflow tract of the left ventricle again opposes this rotation Thus it happens that the right ventricle not only fills the waistline progressively but forms the main part of the left cardiac border down to and including the apical area Instead of the normal concavity the left heart border appears convex with the lower part of the left border extending almost perpendicularly toward the apex which is situated at its normal place *(figure 30)* *This form of the* heart is so characteristic that one may speak of a mitral *stenosis configuration* (*Holzmann*)

Although the left atrium normally is situated posteriorly it becomes visible at the right border of the heart in about 50 per cent of the cases with mitral stenosis this is due to rotation of the heart and to enlargement of the left atrium Sometimes the left atrium bulges far into the right lung field and a double contour is formed due to the superimposition of the right and left atrium (figure 29) The left atrium may be visible at the right *and* the left cardiac border (figure 31)

If the left lower heart border runs obliquely to the left the mitral stenosis is combined with some lesion which causes an enlargement of the left ventricle Usually this will be a mitral insufficiency but occasionally an aortic insufficiency or hypertension will be responsible

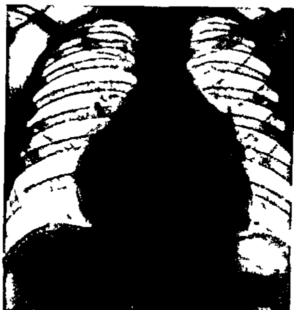


FIG 30 Mitral stenosis configuration in a patient with rheumatic mitral stenosis



FIG 31 Giant left atrium in a patient with rheumatic mitral stenosis The left atrium forms a great part of the left and right cardiac border The lung fields are clear

The huge proportions of the atrium in some cases of mitral stenosis are remarkable One case is known in which it had a capacity of three liters (Minkowski) An enormously dilated atrium may fill the right chest and may be confused with a right sided pleural effusion Even moderate dilatation of the left atrium can produce left paravertebral dullness between the third and eighth dorsal vertebra It may erode the vertebrae It should be stressed however that a very large left atrium is encountered more often in mitral regurgitation than in stenosis An unusual degree of dilatation which at times is encountered even with a slight mitral stenosis is clearly not due to dynamic factors alone An old carditis with fibrosis of the atrial wall plays an important part

A markedly dilated left atrium forms a large blood depot and acts like an enlarged liver in diminishing pulmonary congestion and dyspnea even in an advanced stenosis

Due to the rotation of the heart and the diminishing output the aortic knob tends to disappear in the mitral heart this happens especially when the mitral stenosis is acquired in early childhood The dilated pulmonary artery and conus also push back the aorta (Zdansky)

The increased pressure within the lesser circuit causes the hilar markings to enlarge but they are sharply outlined Pulsations are strong and may equal those observed in the 'hilar dance' seen in defects of the ventricular septum pulmonary regurgitation persistent ductus arteriosus fever and hyperthyroidism

(3) Marked dilatation of the inflow tract of the right ventricle finally develops The apical impulse becomes palpable beyond the midclavicular line and the cardiac shadow enlarges to the left and to the right (figure 29 b) dilatation of the right atrium causes a distinct dullness to the right of the lower sternum

If the myocardium is damaged this third stage is reached even before the valvular lesion becomes very advanced with a normal myocardium however this stage appears late

Auscultation

Auscultation reveals a very loud accentuated sometimes tympanitic or bell like first heart sound in the region of the apex There are two reasons for this accentuation (1) the mitral valves are changed by increased amounts of connective tissue and lime salt deposits (2) the filling of the left ventricle is diminished

Vibrations due to the valvular closure and systole are apparently intensified if the filling of the ventricle is diminished empty barrels make the most noise Actually a very loud first heart sound is heard during syncope and sometimes in shock when the content of the left ventricle diminishes A loud first sound is heard when the heart is overactive as in hyperthyroidism or cardiac neurosis This occurs not only as the result of hyperactivity but also because the tachycardia regularly present in these conditions shortens diastole and diminishes ventricular filling A loud first heart sound is also noted in extrasystoles when the premature contraction occurs very early in diastole

Another explanation of the sharp first sound is the abrupt intra atrial displacement of the leaflets which have decreased length and mass (Nichols et al)

The accentuation of the first heart sound will be absent when the left ventricle fills sufficiently due to an accompanying mitral or aortic insufficiency It is also absent when the valves are calcified and not flexible The change of the first heart sound is rarely the sole basis for the diagnosis of mitral stenosis Often however it is a finding leading to a careful examination which will reveal the diagnosis

In the phonocardiogram a delay of the appearance of the vibrations of the first heart sound is found (Cossio and Berconsky) Instead of appearing about 0 04 second after the beginning of the QRS complex in the electrocardiogram they appear after an interval of 0 08 second or more (figure 33 a)

In very early mitral stenosis murmurs may be absent and pure sounds are heard The valvular alterations are too trivial to create abnormal eddies and murmurs Nevertheless a murmur may appear in these cases if the examination is conducted immediately after exertion or after the inhalation of amyl nitrite (Morrison test)

Generally speaking a murmur may appear or may become louder *first if* the stenosis becomes greater (this cannot be produced artificially) or second if the velocity of blood flow is accelerated by exercise or amyl nitrite

The murmur appears first at the end of diastole that is in the presystolic period This presystolic murmur seems to begin softly then gradually become louder ending in the accentuated first heart sound (figure 32 a) It is called the presystolic crescendo murmur Actually graphic records reveal that this murmur is often continuously of the same intensity the crescendo character is often an auditory impression due to the sound immediately following the murmur (Lewis)

The ventricle is filled from the atrium chiefly during the initial phases of diastole Therefore it is striking that the murmur of mitral stenosis is often heard only at the end of the diastole presystolic rather than at the beginning The reason is as follows filling of the ventricles in the beginning of diastole depends mainly upon the influx of blood when pressure in the atrium and ventricle differ Late in ventricular diastole however the atrium contracts increasing the speed of flow enough to produce a murmur in the case of a slight mitral stenosis Thus in this instance as well as in many others the velocity of blood flow is responsible for the development of a murmur

If the stenosis of the mitral valve progresses the inflow *of blood in the* earlier phases of diastole also produces a murmur and this is truly decrescendo it is loud at first since intra atrial pressure is higher at the beginning of diastole and the blood flows speedily into the ventricle Later in diastole atrial pressure diminishes and the murmur becomes softer It often vanishes momentarily until the atrial contraction causes the presystolic murmur to occur Occasionally one murmur merges directly into the other especially when the rate is fast so that all diastole is occupied by the characteristic rumble In this stage one

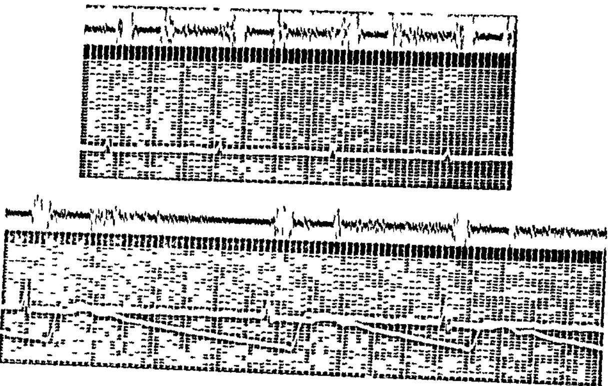


FIG 3 (a) Mitral stenosis with sinus rhythm Stethogram from apical area with a crescendo presystolic and a diastolic murmur A faint systolic murmur indicated the presence of a mitral regurgitation (b) Mitral stenosis and atrial fibrillation at the apical area a prolonged diastolic murmur was audible in addition to a soft systolic murmur

hears the classic *flout tataran* of Duroziez which is more closely approximated by *rrt tataran*

Thus an increase in the degree of mitral stenosis may intensify the murmur in certain stages At the beginning of a mitral stenosis all murmurs may be absent during rest Later a presystolic rumble is audible and finally a murmur appears in the early part of diastole as well At any time however the common complications of mitral stenosis to be discussed presently may develop and the murmurs disappear Therefore patients with loud murmurs are encountered more often in private practice and in out patient clinics among the ambulatory group than in those confined to hospital wards

The first murmur to vanish the murmur which disappears sooner or later in the course of every mitral stenosis is the presystolic murmur Since it develops from an accelerated inflow of blood produced by atrial systole it vanishes when the left atrium ceases to contract normally There are two reasons for this disappearance

(1) Marked overdistention of the left atrium makes the presystolic murmur vanish The ventricles are composed chiefly of muscle fibers with a few interspersed connective tissue and elastic fibers the atria however are formed by a network of small muscle bundles the meshes of which are filled with considerable fat and connective tissue Pronounced dilatation of the left atrium soon overstretches these bundles and reduces their contractile power From the standpoint of cardiac dynamics overdilatation of the atrium means paralysis of this chamber Such an atrium acts chiefly as a reservoir and does not assist in the propulsion of blood Thus with progressive dilatation of the left atrium the presystolic murmur becomes ever shorter until it vanishes completely If a loud drawn out presystolic murmur is still audible certainly the left atrium is not markedly dilated and is able to perform valuable work in compensating the valvular lesion If on the other hand a case of mitral stenosis with regular cardiac action comes under observation and no presystolic murmur is detected it is justifiable to infer the presence of marked left atrial dilatation from this finding alone Usually this is confirmed by fluoroscopy

(2) The second cause for the disappearance of the presystolic murmur is atrial fibrillation (figure 32 b) In fibrillation so many stimuli are formed in the atrium (approximately 600 per minute) that coordinated contraction ceases The atria show very rapid scarcely visible remarkably feeble movements and therefore as far as the dynamics are concerned one may speak of a paralysis of the atria With the onset of fibrillation the presystolic murmur vanishes This event occurs sooner or later in most cases of mitral stenosis

The murmur that appears in early diastole does not owe its development to the atrial contraction and therefore remains during atrial fibrillation just as it persists when the left atrium is greatly dilated In some cases however the presystolic murmur disappears at a time when no diastolic murmur was present In this instance the lesion becomes mute or silent

Since ventricular rhythm is completely irregular in atrial fibrillation and repeatedly one beat follows another after a very short diastole the diastolic murmur may appear just before the first heart sound of the following beat in this case it may seem to develop a crescendo character and may simulate a presystolic murmur This explains the recurrent but erroneous report that presystolic murmurs are heard in spite of fibrillation If such patients are digitalized and diastole is lengthened by slowing of the rate one can readily be convinced that the murmur is purely diastolic (figure 32 b)

Some believe that the presystolic murmur of mitral stenosis originates not from the atrial contraction but rather from ventricular activity and that it is a systolic phenomenon Graphic registration and the observation of the same presystolic murmur in 2 1 atrioventricular block even during the atrial systole which is not followed by a ventricular contraction prove that the murmur is actually caused by the atrial contraction

The silent (mute) type of mitral stenosis is not limited to early cases nor to those cases in which the presystolic murmur disappears before the diastolic murmur has appeared The diastolic murmur may also vanish as the lesion progresses if the valvular ring becomes rigid calcified and narrower (tight mitral stenosis) The flow of blood into the ventricle becomes progressively slower until the blood merely trickles into the chamber when the velocity of blood flow diminishes enough the murmur disappears

Under all these circumstances the lesion must be recognized by other signs by palpation and percussion in particular The silent type of mitral stenosis is not rare and probably about 50 per cent of the cases observed for a sufficiently long time are temporarily silent The characteristic history of increasing exertional dyspnea in the absence of nocturnal dyspnea facilitates the diagnosis

Too often however the lesion is considered silent even though murmurs are present for the murmurs are not detected when certain rules are disregarded These rules should be followed diligently in the auscultation of these cases

The murmurs of mitral stenosis almost without exception are not widely transmitted While other murmurs even if moderately loud are heard in several places or even over the entire heart the murmurs of mitral stenosis are audible only in circumscribed areas They vanish if the stethoscope is shifted only a little For this reason the apical area must be examined very carefully point by point when mitral stenosis is suspected Most frequently the murmur if present is found at the area of the apical impulse Occasionally it is heard outside of the apex beat nearer to the axillary line and in rare cases inside nearer the left sternal border In mitral stenosis only relatively slight differences in pressure within the cardiac chambers are involved the murmurs are therefore never exceedingly loud

Very often the murmur like the thrill is perceptible only when the patient assumes the left lateral position Auscultation in this position should never be omitted when mitral stenosis is suspected and no murmurs are heard in the supine posture The murmurs of mitral stenosis are also often overlooked when patients

are examined while they are standing For this reason instances of mitral stenosis are often missed in school examinations and other routine health surveys in which the examining physician listens to the heart only while the patient is in the erect posture

Another reason for missing the murmurs of mitral stenosis is that they present peculiar qualities Owing to their low pitch these murmurs sound quite different from other murmurs The murmurs are rough uneven and give the impression of a short rumble or a few split sounds rather than of gushing and flowing of liquid in the manner of other murmurs If the murmur is very brief it is particularly difficult to differentiate from an impure sound Thus students frequently report having heard no murmur in a given case — until they learn that the rough rumble they noted was the characteristic murmur of mitral stenosis Undoubtedly some experience is necessary in order to recognize this particular diastolic murmur

In some cases the diastolic murmur of mitral stenosis must be distinguished from a diastolic murmur of aortic insufficiency As has been pointed out both murmurs may be heard at the apical area Quite often in pulmonary emphysema for example it is audible only at this place The physical findings in a pure aortic insufficiency to be sure differ vastly from those in a pure mitral stenosis At the beginning however and before characteristic physical signs develop or when mitral and aortic valve involvement are combined it is not always easy to decide whether the apical diastolic murmur is due to mitral stenosis or aortic insufficiency The low pitched rumble of mitral stenosis is not always sufficiently pronounced to permit differentiation

In an insufficiency of the aortic valve the diastolic murmur immediately follows the second sound since high intra aortic pressure causes an immediate regurgitation of blood into the left ventricle through the incompetent valve In a mitral stenosis the diastolic flow of blood from the left atrium into the ventricle encounters an obstruction resulting in a diastolic murmur The left atrial pressure however is considerably lower than the intra aortic pressure Until the mitral valve opens and the pressure in the ventricle is sufficiently low to permit the blood to flow from the atrium to the ventricle an interval elapses Hence the murmur of mitral stenosis does not follow the second sound immediately as in the case of aortic insufficiency it appears after an easily perceptible interval which separates it from the second sound While a bipartite rhythm (to and fro murmur) is heard in aortic insufficiency it is tripartite in mitral stenosis In the latter one hears the loud first sound (and a systolic murmur since a mitral insufficiency often coexists) then the second sound and finally after a short pause there is the diastolic murmur of mitral stenosis This triple event closely resembles gallop rhythm particularly when the diastolic murmur is very short and rough and thus difficult to differentiate from a heart sound

The second pulmonic sound is often accentuated Increased pressure within the lesser circuit is advanced as the primary factor in the accentuation since this causes more forcible closure of the valves There is however another very important mechanism dilatation of the conus of the right ventricle and of the

pulmonary artery brings these structures nearer to the thoracic wall so that the second sound is conducted better to our ear Just as a dilated ascending aorta transmits the diastolic murmur of aortic insufficiency better to the second right intercostal space so the dilated pulmonary artery and pulmonary conus conduct the second pulmonic sound better to the left Actually this accentuation is not heard best nor is the shock due to the closure of the pulmonic valves felt best in the area of the actual location of the valves rather one hears and feels the second pulmonic sound where the wall of the conus or pulmonary artery comes in contact with the thoracic wall This is usually in the second or third interspace along the left cardiac border

An accentuated second pulmonic sound is not invariably found in mitral stenosis As long as the pressure within the lesser circuit is not elevated — as long as the left atrium compensates the stenosis perfectly — the second pulmonic sound is normal A previously existing accentuation may disappear if the pressure in the lesser circuit falls owing to the appearance of right ventricular failure On the other hand young individuals occasionally up to the age of twenty five often show a distinct accentuation of the second pulmonic sound in the absence of a mitral lesion In youth the pulmonary artery physiologically is wide and prominent it lies near to the thoracic wall so that the second pulmonic sound is louder than the second aortic sound Beyond the age of thirty five the second aortic sound normally becomes slightly louder

These facts indicate that the importance of an accentuated second pulmonic sound in the diagnosis of a mitral lesion has been overrated in the past

Apart from an accentuation a splitting (duplication) of the second pulmonic sound is found This phenomenon is also observed in healthy young people Although a final explanation is not as yet available many believe that the duplication is due to an asynchronous closure of the aortic and pulmonic valves This explanation seems logical since in mitral lesions the increased pressure in the lesser circuit should cause the pulmonic valves to close earlier Normally both shut at the same time despite the fact that the aortic pressure is approximately six times as high as the pulmonic pressure If this explanation were exclusively valid the duplication should be heard distinctly over the aorta as well whereas it is actually found only over the pulmonic area Therefore it is possible that the individual pulmonic valves themselves do not close simultaneously The dilated conus of the pulmonary artery with its ostium thrust forward by the dilated left atrium might be partly compressed by the anterior chest wall so that the three pulmonary valves no longer lie in the same plane and no longer close simultaneously Against this explanation is the fact that very slight differences are involved which are scarcely perceptible to the human ear However not rarely the duplicated second sound is palpable in the form of a short circumscribed double shock exactly over the pulmonary area that is at the place where it may arise

The *opening snap* (claquement d ouverture de la mitrale opening click) is a phenomenon which is heard in a majority of patients with mitral stenosis

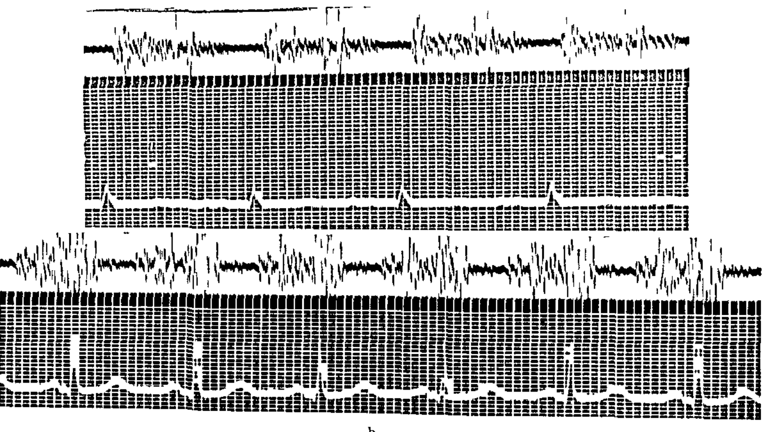


FIG 33 (a) Mitral stenosis and regurgitation with sinus rhythm There is a systolic and diastolic murmur with an opening snap (b) Tracing obtained from a 38 year old woman with rheumatic mitral stenosis there is a soft systolic apical murmur and a rumbling diastolic one with an opening snap of the mitral valve

(figure 33) It is a short high pitched sound which appears in the phonocardiogram 0 09 to 0 13 second after the beginning of the second heart sound It coincides with the peak of the V wave in the phlebogram Others claiming that this interval should be shorter than 0 08 second speak of a third heart sound when it amounts to 0 12 second or more (Ongley et al) It is rarely found over the whole heart usually appearing on the left lower sternal border or about halfway between the apex and left sternal border It is also present in atrial fibrillation It is absent in patients with a very mild stenosis of the valves and when the valves are markedly calcified It is also absent when mitral regurgitation predominates These facts have great importance in the evaluation of a patient for surgery The opening snap is heard best with the patient in the supine position The diastolic murmur is separated from the opening snap by a very short interval Often the snap is hidden from our ears in the murmur Its relation to the second sound varies with the length of the preceding diastole If this is short the closure of the mitral valve is delayed and the time interval between the second sound and the snap is shorter The distance between the second heart sound and the snap depends on the height of left atrial pressure The phenomenon is explained by the sudden tension of the fused mitral valves at the beginning of diastole when the downward movement of the valves is suddenly inhibited

It is higher in pitch and shorter in duration than the second sound or the third heart sound Monsey found an opening snap on 28 of 33 patients with mitral stenosis

Systolic Pulmonary Murmurs Not rarely these patients exhibit a systolic murmur at the pulmonic area Occasionally this murmur may be very loud and rough it may even be associated with a thrill and may dominate the auscultatory picture As a cause of this murmur the previously mentioned compression of the pulmonary artery by the anterior chest wall has been advanced (functional supravalvular pulmonary stenosis) Another and in our opinion better explanation is based upon the fact that in mitral stenosis both the right ventricle and pulmonary artery are dilated so that the valve ring whose diameter is normal acts as a relative stenosis

Diastolic Pulmonary Murmurs Occasionally there is a high pitched diastolic murmur to the left of the sternum in the fourth or fifth interspace this is due to a relative pulmonary insufficiency The murmur and its mechanism will be discussed later

Angiocardiography

Angiocardiography has been recommended as a diagnostic method for the selection of patients for surgery In advanced mitral stenosis prolonged and dense opacities are found in the left atrium while the left ventricle is not opacified to the same degree

Electrocardiography

This may aid in diagnosis The P waves are often abnormally wide (more than 0 12 second) and they are slurred in leads I and II (figure 8 a) There is often a right axis deviation and in more advanced cases evidence of right ventricular hypertrophy (the PS—T segments and T waves are directed opposite to the main deflection) (figure 13) The R waves in V2 are often higher the S waves in V5 and V6 deeper than normal The T waves in V2 and V3 are often inverted When the left ventricle is also affected due to a mitral insufficiency aortic insufficiency left axis deviation or no axis deviation is found In such cases the P waves changes alone are significant Atrial fibrillation is common

Differential Diagnosis

The low pitch of the murmurs in mitral stenosis makes them sound very much like an impure or split heart sound — a common source of error

Experience shows that physicians who become interested in heart diseases for some time make the diagnosis of mitral stenosis too often because they diagnose the lesion in every case exhibiting an impurity of the first heart sound at the apex A presystolic murmur is believed to be present when the first heart sound is split especially when the vibrations of the first part are softer than those of the rest of the first heart sound Splitting of the first heart sound often depends upon an audibility of the atrial sound this is a common event in the hyperexcitable heart of hyperthyroidism and cardiac neurosis It is not rare in an advanced anemia and was common when the treatment of pernicious anemia was restricted to arsenicals and iron Duplication of the first sound also occurs in kyphoscoliosis and pleural adhesions Since the first heart sound is abnormally loud in most of the aforementioned conditions confusion with mitral stenosis is possible Splitting of the first heart sound at the apical area also appears in some congenital heart lesions (patent ductus arteriosus atrial septal defect) as well as in hypertension and coronary sclerosis To be sure these cases lack the long drawn out presystolic rumble and present only a brief impure sound be fore the first heart sound but the same acoustic phenomenon is also found in mitral stenosis

The Austin Flint murmur wrongly believed by many to be common has been discussed above It may be either presystolic or early diastolic Since the left atrium is dilated in these cases and the second pulmonic sound may be accentu ated distinction from an actual mitral stenosis is often impossible during life

Diastolic murmurs of the same origin have been described in patent ductus arteriosus and in atrial septal defects In the latter this murmur leads to the wrong diagnosis of Lutembacher s syndrome It has also been observed in active rheumatic fever It is explained by the whirlpools created by the inflow of blood into the dilated left ventricle

Occasionally the acoustic phenomena caused by the atrial contraction in partial atrioventricular block are confused with the murmurs of mitral stenosis

A mid diastolic rumble like that of mitral stenosis is present in many cases of 2 1 block The sound caused by the atrial contraction is often double or split This produces the very close resemblance to a diastolic rumbling mitral murmur

The clinical picture of mitral stenosis is imitated by myxoma of the atria, particularly the left one With angiocardiography the diagnosis is possible during life because of the constant presence of a filling defect in the atrium (Steinberg et al)

These imitations of the murmurs of mitral stenosis as well as the fact that real organic mitral stenosis often presents no murmurs for some time make the diagnosis of some cases of mitral stenosis more difficult than is commonly realized

Complications

Atrial Fibrillation This is one of the most common complications in the course of mitral stenosis It is usually present in the more advanced cases on the hospital ward but it may appear at any time even in the very early stages of the lesion

The disturbance of the circulation due to atrial fibrillation will be discussed in a later chapter In regard to mitral stenosis the increased rate so often appearing at the onset of fibrillation and the disappearance of effective contractions of the left atrium are harmful Many cases of mitral stenosis begin to show evidence of decompensation with the onset of atrial fibrillation

The fact should be stressed however that atrial fibrillation proves a useful complication in other cases of mitral stenosis and may serve to make life more tolerable and even to prolong it As long as sinus rhythm prevails in a compensated mitral stenosis the rate is often very high and may reach 120 beats per minute Since a longer diastole is necessary in mitral stenosis to permit blood to pass through the stenotic valve this tachycardia serves to increase congestion within the left atrium and the lesser circuit Digitalis does not slow such hearts in fact there is no beneficial treatment available for these patients except mercurial diuretics which somewhat diminish the fluid content of the lungs and relieve dyspnea and orthopnea In such cases the appearance of atrial fibrillation affords great relief It is true that the fibrillating atrium is unable to contract effectively and cannot help compensate the lesion this fact is of no consequence however because the left atrium is usually overdilated in the first place and therefore without significance from the standpoint of dynamics In fibrillation with mitral stenosis digitalis can slow the heart to such a degree that the length of diastole almost doubles Therefore pulmonary congestion quickly diminishes and patients may live comfortably for years

Undoubtedly many patients live to reach the button hole stage of mitral stenosis only because atrial fibrillation occurred

Before atrial fibrillation is established patients sometimes pass through a stage of paroxysmal fibrillation in which the attacks last a few minutes hours or days In this instance treatment may be difficult because the attacks do not

recur sufficiently often for preventive treatment with quinidine nor do they last long enough to permit the use of digitalis With a longer duration of the attacks of paroxysmal fibrillation and when the physician has the impression that the patient would be better off with sinus rhythm 0 20 Gm quinidine sulphate is given every two hours until the attack subsides But when atrial fibrillation has been definitely established in cases of mitral stenosis there is rarely an indication for abolishing it by quinidine

Mural Thrombi and Embolism Not uncommonly mural thrombi form in the dilated left atrium especially if atrial fibrillation is present They are not the result of a stagnant circulation alone but are usually due to involvement of the atrial endocardium by the rheumatic process this often causes deposits of fibrin as well as the formation of thrombi at the affected area

Detached fragments of such thrombi may produce vascular accidents such as cerebral embolism or embolism in a peripheral artery The middle cerebral artery is often affected by such emboli In a series of 72 cases of mitral stenosis with cerebral embolism atrial fibrillation was present in 55 (Harris and Levine) Recovery from a cerebral embolism sometimes progresses with astonishing speed and to a surprising extent

It has been established that peripheral embolism occurs in 5 to 10 per cent of cases of mitral stenosis After the first embolism occurs the physician is confronted with the problem whether to use prophylactic therapy with anticoagulants Because of the necessity to maintain a certain critical prothrombin level the dangers of such therapy and the rarity of recurrences this treatment is utilized only for special patients exhibiting frequent embolic manifestations Embolism occurs in spite of correctly guided therapy with anticoagulants

Tuberculosis The frequently encountered statement that pulmonary congestion in mitral stenosis protects the patients from pulmonary tuberculosis is not justified It seems that pulmonary tuberculosis in patients with mitral stenosis is as common as in the general population

Pulmonary Hemoptysis This complication has various causes It may appear in pulmonary embolism with infarction it is seen in acute pulmonary congestion or in pulmonary edema It is observed even in the presence of atrial fibrillation Sometimes amounts up to 500 ml of blood are expectorated at one time A leukocytosis and mild fever may be present The patient may complain of precordial distress The lung fields show mottling roentgenologically A rupture of pulmonary veins or varices of the bronchial veins may be responsible

Ball Thrombus A rather rare and interesting complication is a ball thrombus in the left or rarely right atrium This thrombus may be sufficiently large to fill the entire atrium The true ball thrombus is free or may be attached to the atrial wall by a pedicle Atrial fibrillation is usually present The clinical diagnosis of this complication sometimes is possible since the thrombus very markedly disturbs the circulation and causes certain characteristic signs Angiocardiography demonstrating a filling defect in the atrium may help These patients usually have deep cyanosis and severe dyspnea the peripheral parts of the body

especially the feet and legs are cold the peripheral pulses are almost impercep tible and gangrene develops in the toes fingers nose and ears This gangrene is often symmetrical because the minute volume undergoes extreme reduction due to the obstruction of the mitral orifice It would be asymmetric if the gangrene were the result of embolism which sometimes appears in the peripheral arteries The evolution of symptoms from the initial coldness of the extremities to pallor lividity necrosis and gangrene may require weeks

In addition to these permanent features transient complications may follow temporary impaction of the ball thrombus in the mitral orifice Such patients have attacks of fainting and disturbances of speech or paralysis of the limbs Disorientation and convulsive seizures occur if the impaction lasts longer Natu rally prolonged block of the mitral orifice is fatal

In one of our cases (Lans) with the picture just described large thrombi practically filled the whole atrium and obstructed the orifices of the pulmonic veins to a great degree The presence of a ball thrombus is thus not necessary for this clinical syndrome to appear

Obviously the prognosis of these patients is poor A duration of life exceed ing one month after the appearance of symptoms is apparently rare Atrial fibrillation in the absence of mitral stenosis is rarely associated with the forma tion of a ball thrombus but such cases have been observed in hypertension We saw a somewhat similar syndrome as a consequence of a ball thrombus in the right atrium Surgery for removal of the thrombus should be contemplated

A similar picture may be found in atrial myxoma where the glossy gelatinous tumor may fill the whole left atrium These tumors histologically have a structure like Wharton s jelly of the umbilical cord They appear in hearts without mitral stenosis and represent the most common primary new growth of the heart

Laryngeal Nerve Paralysis A paralysis of the left recurrent laryngeal nerve causing hoarseness sometimes occurs Originally this phenomenon was explained by a compression of the nerve between the enlarged left atrium and the arch of the aorta It seems however that the nerve is squeezed between the aorta and left pulmonary artery when the latter is pushed forward by the enlarged left atrium

Paralysis of the left recurrent laryngeal nerve due to a similar mechanism has also been described in connection with left ventricular failure (King et al) Improvement has been observed following mitral surgery (Ari et al)

Dysphagia This is an occasional result of the marked dilatation of the left atrium Posterior displacement of the esophagus is usually accompanied by a lateral displacement (in most cases to the right) so that the esophagus usually but not invariably escapes compression

Dysphagia also occurs in pericarditis with effusion in rare cases of left ventricular enlargement (aortic stenosis) in anomalies of the aortic arch and of the large arteries originating from the aorta (dysphagia lusoria) and saccular as well as dissecting aneurysms the three conditions mentioned last are provocative most often

Bronchial Stenosis Since the left atrium is situated just beneath the tracheal bifurcation atrial enlargement may increase the angle of the bifurcation The angle of the two main bronchi is normally about 70 degrees and always less than 90 degrees In mitral stenosis it may increase to 110 degrees It is the left main bronchus which tends to be pushed upward as the tissues are softer in children compression of the left main bronchus in mitral stenosis can occur and may cause pulmonary atelectasis

Pulmonary Edema The mechanism of this lesion has been explained in the first chapter It is often missing for reasons explained above

Prognosis

The prognosis in patients with rheumatic mitral stenosis in general depends upon many factors not the least of which is the frequency of recurrences of rheumatic fever and the condition of the myocardium When mitral stenosis is observed early in the course of rheumatic fever or after the active phase is over it may seem very slight and therefore the outlook may appear good But gradually and apparently without new attacks of rheumatic fever which can be diagnosed clinically a button hole mitral stenosis may develop and the patient succumbs within a few years At other times the lesion remains minimal and stationary these patients lead almost normal lives and reach old age Some live out their lives without being aware that heart disease exists

Despite such exceptions the average age at death from mitral stenosis is near forty years Most of these patients ultimately seek hospitalization for congestive failure

Surgical Therapy of Mitral Stenosis

The statements encountered in current literature in particular literature of surgical origin that mitral stenosis is essentially a surgical disease is a great simplification of the issue although it may be conceded that in certain stages medicinal therapy has little to offer This is true not only in advanced cases but in some patients even early when the heart is scarcely enlarged and the right ventricle functions perfectly but the pulmonary congestion is tremendous because of the mechanical obstacle of the stenotic mitral valve Here digitalis is of little help while surgery miraculously relieves the attacks of pulmonary edema dyspnea and hemoptysis

The idea of surgical relief is not a new one Sir Lauder Brunton suggested it long ago and Suttar performed the finger fracture procedure as early as 1925 The following year Pribram performed the operation from the ventricle Since procedures advised at that time resulted in a detrimental mitral insufficiency a high mortality and rare improvement operations were soon discontinued

Different Surgical Procedures Other surgical procedures were recommended all designed to diminish pulmonary congestion Bland and Sweet recommended an anastomosis between the right inferior pulmonary vein and the vena azygos Cossio and Perianes recommended tricuspid valvulotomy from the jugular vein

to create a regurgitation and relieve pressure in the lesser circuit and Cossio also ligated the inferior vena cava to reduce the right heart output others performed a sympathectomy to slow the heart All these efforts were soon overshadowed by two operations which proved safer since they did not usually create an appreciable insufficiency of the mitral valve mitral commissurotomy and the finger fracture method In both procedures one opens and enters the left atrium The finger fracture method is preferred if it is impossible commissurotomy is done With both methods the individual leaflets are separated no valvular tissue is removed but the orifice is enlarged

Indications and Contraindications Patients with mitral stenosis are divided into four groups or stages In stage I the lesion is asymptomatic In stage II the patient has symptoms at rest or effort but the complaints are static and do not progress In stage III the symptoms progress in spite of correct therapy In stage IV the complaints are incapacitating No operations are performed in stage I and they are seldom of use in stage IV they are indicated and useful in stages II and III These stages of course represent a rough distinction only A patient may show progressive complaints and failure (stage III) but the stenosis of the mitral valve is slight and not advancing however the myocardium is damaged by rheumatic fever and fails We recommend the operation in stage II only if pulmonary edema or hemorrhage is present or if the complaints are marked Stage III i e in progressive disease offers the chief indication but one must be sure — if possible — that progression of complaints is not caused by reactivation of rheumatic fever acute infection overexertion and so forth

The operation is not performed too early in childhood since mitral stenosis tends to be progessive and new deposits of fibrin repeatedly develop on the valves due to recurrences of rheumatic fever Successful postoperative cases are known in which the benefit of operation disappeared after a few years because the stenosis recurred Therefore although active rheumatic fever is a contraindication it is clear that this rule is too dogmatic In the first place signs of rheumatic activity have been found in 30 to 40 per cent of postoperative patients in the resected left atrial appendices In most instances no clinical evidence of activity existed Moreover if a patient with mitral stenosis congestive heart failure and active rheumatic fever is operated on the diminution of only *one* of these factors may be life saving

Subacute bacterial endocarditis is also a contraindication Operation is contraindicated in patients with marked irreversible cardiac dilatation One does not operate on patients having an appreciable aortic stenosis and regurgitation or a definite mitral insufficiency Studies with the gloved finger during operation have shown that mitral insufficiency causes a regurgitating jet and that its presence of a slight degree does not contraindicate the operative procedure while a definite mitral regurgitation does The difficulty of diagnosing a mitral insufficiency will be discussed in the following section

We advise the operation in patients with increasing disability According to Wood surgery is required in 50 per cent of all patients with mitral stenosis

Since after the age of twenty years recurrences of rheumatic fever are less common some physicians prefer to operate on patients under 20 In patients over 40 years old complications occur more often and the mortality increases

The patient should be digitalized before the operation neither atrial fibrillation nor a history of pulmonary embolism is a contraindication However the operation cannot always be carried out since occasionally the atrium is filled with thrombi Surgery is not advised if there is no evidence of an increased resting pressure in the pulmonary arterial system or when one suspects that pulmonary pressure is increased because of left ventricular failure (Cournand et al)

Results of Operation The operative mortality varies according to the surgeon and to the stage in which the patient is operated on Thus in one series no patient died in stage II while 4 6 per cent died when the operation was performed in stage III the immediate operative mortality in stage IV was 31 per cent The average mortality is reported as between 6 6 and 27 4 per cent Embolism in the systemic circulation occurred in 6 per cent of the operations Harken reports a mortality of only 1 per cent in patients in stage III while it was 27 per cent in stage IV

A serious complication is a systemic embolism from dislodged thrombi in the left atrium At the present time owing to Bailey s method of compressing the carotid arteries and permitting the blood to gush out and carry the thrombotic material with it the incidence is somewhat diminished But many surgeons abandoned this procedure A rare but serious complication is dissection of the left circumflex coronary artery or subacute bacterial endocarditis caused by staphylococci (Dalton et al)

While the operation brings dramatic relief in some cases it lacks success in others Prediction is impossible at present The operation is rarely curative however In 214 patients one group of surgeons saw 41 6 per cent greatly improved 7 per cent improved and 13 0 per cent unimproved Bland reports an improvement varying between 58 3 and 86 9 per cent The salvage rate of surgery in class IV patients according to Denton and Bolton is as follows there was an immediate mortality of 12 of 61 patients nine died within one month Of 38 living patients 33 showed distinct improvement

No proof has been given that mitral surgery diminishes the incidence of systemic embolism Despite marked clinical improvement the change of heart size and shape and of the electrocardiogram are often insignificant An improvement may appear 4 to 6 months following surgery Disappearance of the increased pulmonary resistance seems to require time

Clover examined 50 patients five years after the operation In 20 the results were excellent 16 were improved and 5 unimproved The others had died Baker et al found the results in 18 out of 45 postoperative patients not favorable three years after the operation

The final results — the frequency of re stenosis the ultimate effect of surgery as to duration of life — cannot as yet be evaluated

The diastolic murmurs may become shorter or may disappear Even if they remain unchanged improvement may be great The size of the heart may diminish or increase the latter because of the better filling of the left ventricle The first heart sound over the apex and the second pulmonic sound may be less accentuated after successful surgery

Ideal Subject The ideal subject for surgery has a snappy apex beat and a very loud apical first sound (which disappears in an appreciable mitral regurgitation) There is a clearly audible opening snap (which disappears in marked regurgitation in rigid calcified valves which respond poorly to surgery and finally in marked pulmonary hypertension) In mitral regurgitation an audible third heart sound replaces the opening snap (Wood) The aortic knob is absent and the left ventricle not large There is typical widening and slurring of the P waves in leads I and II

Postcommissurotomy Syndrome An interesting complication of the operation is the postcommissurotomy syndrome which appears a few weeks after surgery The incidence of this syndrome has been found to be around 24 per cent It is known that rheumatic fever may be reactivated after trauma In the syndrome the patient develops joint and chest pain fever leukocytosis pericarditis and pleurisy While some authors believe that pulmonary emboli and the pericarditis which follows every entry into the pericardium even under sterile conditions are responsible we think that the appearance of a prolonged P—R interval in the electrocardiogram of some of these patients and the occasional marked increase of the antistreptolysin titer favor the assumption of a recurrence or reactivation of rheumatic fever Dressler calls attention to the striking resemblance between idiopathic pericarditis and the postcommissurotomy syndrome Different mechanisms may be responsible in different cases

Pathophysiology The contributions of surgery to better understanding of the pathophysiology of this lesion are considerable

Astonishing was the finding that in most patients examined by surgeons the size of the mitral orifice was 1 square cm or less The cardiac output may fall to 2 liters per minute or less (Dexter et al) Even in patients who were asymptomatic (stage I) the orifice was found so small that the fingertip could not pass through it even orifices of 0 3 square cm have been seen Surgery is very successful even if it increases the diameter only to 1 5 square centimeters This is remarkable because one would have assumed that some patients with a damaged myocardium develop cardiac failure in earlier stages In any event in agreement with experimental findings and in analogy with the aortic orifice reduction of the mitral orifice to one fourth normal which is about 1 square cm seems to be the critical value Under these conditions the pressure head necessary for adequate filling of the left ventricle must be considerable

The mechanism of pulmonary hypertension in mitral stenosis has always puzzled clinicians An increased pressure in the pulmonary veins is easily understood Why should this lead to an increase in pressure in the pulmonary arteries? Anatomic changes have been found in the pulmonary arterioles these however

are of a secondary nature the consequence and not the cause of hypertension in the lesser circuit Catheterization revealed that pulmonary vascular resistance rises early in many cases to a multiple of the normal values The mechanism is unknown and reflexes from the dilated pulmonary veins have been postulated We shall see in the chapter on cor pulmonale that local hypoxia in the lung makes pulmonary arterioles contract by a direct action on their smooth musculature Teleologically regarded this narrowing of arterioles may be considered bene ficial since it prevents the appearance of excessively high pressures in the pul monary capillaries and may explain why pulmonary edema is so rare in patients with advanced mitral stenosis It is certainly much rarer than recent reports maintain On the other hand even with mitral orifices of 0 5 square cm normal pulmonary resistance was found so that the mechanism of its development is not clear

Procedure It is the duty of the physician whenever he advises a patient regarding mitral surgery to consider prognosis without surgery the mortality of surgery and the complications of the procedure It is not ethical to tell the patient that he will be cured It is purely fortuitous if the mitral valve regains normal function after finger fracture or commissurotomy Usually the orifice becomes wider by only a few millimeters yet it is astonishing how much improvement such enlargement may bring

MITRAL REGURGITATION

Etiology

Rheumatic Fever Verrucous endocarditis renders the mitral valve incom petent by retracting the thickened leaflets and by shortening the chordae tendineae Rheumatic mitral insufficiency is usually combined with stenosis owing to fusion of the valves Pure mitral regurgitation of rheumatic origin without any evidence of a stenosis is rare Often the stenosis is silent and no diastolic murmur is audible In performing a commissurotomy with the finger in the left atrium Bailey missed the typical regurgitation jet in one third of 1 000 patients Mitral regurgitation is a little more common in men than in women

Relative Mitral Insufficiency Valvular incompetence without organic changes in the leaflets is a very common event in all conditions associated with marked dilatation of the left ventricle It is a typical complication of hypertension aortic insufficiency and myocardial lesions Two forms can be distinguished In one the valvular ring may widen because of a pronounced left ventricular dilatation so that the valves are unable to close in systole In the other and more common variety the heart dilates along the axis of the ventricle this displaces the papillary muscles downward and the chordae tendineae prevent the valves from closing completely

Malformations and Trauma Mitral insufficiency due to malformations or caused by trauma are rare In a traumatic case personally observed by one of us a bullet created a small hole in one leaflet of the mitral valve (Adam)

Atherosclerosis Not rarely atherosclerosis increases the thickness of the aortic leaflet of the mitral valve but this rarely makes the valve incompetent Simon and Liu found calcification of the annulus of the mitral valves in 10 per cent of 590 unselected consecutive necropsies

Dynamics

In mitral insufficiency blood returns to the left atrium under high pressure during ventricular systole In experimental mitral insufficiency more than 50 per cent of the stroke volume may regurgitate

In order to overcome the diastolic intra aortic pressure and to eject its contents into the aorta pressure within the left ventricle must exceed aortic diastolic pressure Due to the loss of blood by leakage through the mitral valve this level of intra aortic pressure is reached later than under normal conditions Since pressure in the left atrium is much lower than that in the aorta it is not clear why the left ventricle does not send its entire output into the atrium According to Wiggers the great vigor of contraction causes intraventricular pressure to rise so rapidly that the resistance of the diastolic intra aortic pressure is overcome The more the myocardium is damaged the weaker the systole and the greater the loss of blood into the left atrium

Symptoms

The complaints are similar to those of mitral stenosis Exertional dyspnea appears early and is the outstanding symptom during the entire course of the disease There are no symptoms specific for mitral insufficiency

Signs

Palpation As in mitral stenosis palpation shows evidence of hypertrophy of the right ventricle as revealed by diffuse pulsations over the precordium The second pulmonic sound may be palpable Early however the apex beat is displaced downward and outward since the left ventricle is dilated from the beginning If the apical murmur is low pitched a systolic apical thrill is sometimes palpable In some patients the unusually large left atrium reaches far into the right chest and systolic pulsations are found to the right of the sternum between the fourth and sixth ribs These pulsations are rather strong owing to the systolic distention of the left atrium by ventricular pressure The proximity of left atrium to the anterior chest wall is favored by the rotation of the heart around its axis to the left

The heart is mitralized with evidence of marked enlargement of the left atrium and left ventricle

Auscultation the Systolic Murmur Auscultation reveals an apical systolic murmur Since murmurs of this kind are often heard in the healthy it is proper to discuss first the systolic apical murmurs encountered in healthy individuals that are so often confused with those of a real mitral insufficiency

The nomenclature is difficult One usually separates the organic murmurs of mitral insufficiency from the functional or ' accidental murmurs of healthy people The term functional is not precisely appropriate for murmurs caused by organic changes also depend upon functional alterations Therefore it has been proposed to differentiate between physiologic and pathologic murmurs Naturally a pathologic systolic apical murmur will not always be due to a mitral insufficiency as there are many other causes for it It has al o been proposed to differentiate between significant and nonsignificant or incidental murmurs

Physiologic murmurs are common In fact many physicians who have reflected on the matter have wondered why a systolic murmur is not heard over every heart under normal conditions When it is recalled how forcibly blood is ejected through narrow ostia into tortuous vessels the usual absence of systolic murmurs is indeed astonishing

Systolic murmurs are quite common in healthy young people Among 218 apparently healthy individuals in the first four decades of life Thayer found a systolic murmur in almost one third Examination of 5541 high school students revealed a nonorganic systolic murmur in 86 63 per cent (Schwartzman) Parkinson and Hartly found systolic murmurs in 10 per cent of healthy recruits Among those not presenting a murmur at rest over 80 per cent develop such a murmur after exercise These murmurs are heard most often over the pulmonary artery and they may disappear in the erect position Sometimes they are very loud and rough but only rarely are they accompanied by a thrill

These physiologic murmurs are less frequent in adults They do however occur at all ages Since a murmur irrespective of its origin depends as pointed out earlier on a certain velocity of the blood flow these murmurs often become louder or appear on exertion *Other physiologic murmurs are audible only* at rest They may be blowing rasping mewing or musical If by chance an opportunity is afforded for the examination of such a heart at necropsy no alteration capable of evoking the murmur may be discovered

Acceleration of the blood flow in anemia or for other reasons may cause a systolic murmur These murmurs appear over all ostia in anemia (Laennec s murmur) and are constantly heard over the base of the heart Formerly they *were accounted for by a diminished viscosity of the blood but undoubtedly* the increased velocity of blood flow is the real causative factor In anemic patients highly musical systolic murmurs may be audible over the large veins near the base of the heart (venous hum) In rare cases the latter are heard even during diastole Loud systolic murmurs (hemic murmurs) and cardiac enlargement in anemic patients may simulate primary cardiac disease

Systolic murmurs appear regularly in fever as the result of increased velocity of blood flow If the fever is of unknown origin a loud systolic murmur over the heart may focus the attention on this organ (a subacute bacterial endocarditis is often suspected) and this may lead to lack of recognition of the real cause for the fever Hyperthyroidism is almost invariably associated with systolic murmurs owing to the acceleration of the circulation

Differentiation between physiologic and organic murmurs is extremely important In patients who have had rheumatic fever in the routine examination of school children in physical examinations for employment for military recruits or for insurance companies the question constantly arises how to interpret a systolic murmur at the base or apex

It is important to remember that every systolic murmur should arouse suspicion This is especially true in the older patient and if it was absent previously Therefore every effort must be made to rule out a pathologic process

Since the differentiation between physiologic and pathologic murmurs concerns a problem that confronts the physician almost daily several methods for arriving at a decision have been recommended

(1) Considerable emphasis has been placed in the past on the fact that murmurs of mitral insufficiency are transmitted to the back while physiologic murmurs are heard only over the heart This rule has little value The transmission of a murmur to the back depends merely on its loudness and its pitch and not whether it originates in an organic lesion of the valve

(2) Levine as pointed out before differentiates six degrees of a systolic murmur It is often stated that murmurs beyond grade 2 are pathologic This is not in accord with our experience It is true that louder murmurs are more suspicious however they are not invariably pathologic Cardiac surgery has also revealed that even in the presence of a grade 3 apical systolic murmur no regurgitating jet could be detected at operation

(3) The absence of the first sound at the apex (occasioned by the mitral incompetency and change in the presphygmic period) has value for the diagnosis of mitral insufficiency if a systolic murmur is audible at the apex Since mitral regurgitation is usually accompanied by mitral stenosis which accentuates the first apical sound this rule often is not reliable

(4) Whereas the physiologic systolic murmur may be very loud the murmur in a true case of mitral insufficiency may be soft and faint The intensity of the murmur does not permit any conclusion concerning the extent of the valvular lesion A slight valvular incompetence is associated with regurgitation of blood through a narrow opening into the left atrium and the murmur may be loud In a more advanced mitral insufficiency the communication between the left ventricle and atrium is broad and sometimes no murmur at all or merely a very faint murmur is audible

One may say that if two patients present exactly the same murmurs over the mitral valve it is entirely possible that one has an organic mitral regurgitation and the other a healthy heart with a physiologic murmur

(5) Considerable stress is often placed upon the accentuation of the second pulmonic sound in mitral lesions This sign is unreliable since it is absent in early stages of mitral regurgitation as long as pressure is not increased in the lesser circuit and is likewise absent in the later stages when right ventricular failure appears with a consequent fall of pressure in the lesser circuit Moreover a loud second pulmonic sound is physiologic in healthy young people Therefore

if such individuals present a loud apical systolic murmur and in addition complain of palpitation and dyspnea an erroneous diagnosis of mitral regurgitation is sometimes made Since the diagnosis of a valvular lesion has a profound effect on the patient and may influence his whole life in many ways this diagnosis should not be made casually Too often one sees patients with healthy hearts in whom the diagnosis of an organic heart disease was made many years ago simply on the basis of a systolic apical murmur



FIG 34 Rheumatic mitral lesion with regurgitation predominating enlarged left ventricle

(6) Frequently it is said that a distinction between physiologic murmurs and those due to mitral insufficiency is possible if the patient is examined in different postures The murmur of mitral insufficiency is loudest if the patient is recumbent while physiologic murmurs are intensified in the erect posture It is true that the murmur of mitral insufficiency as well as those of mitral stenosis often are detected only in recumbent patients Functional murmurs however sometimes have the same peculiarity and therefore no decisive conclusion can be drawn from this fact alone

As a corollary to the preceding discussion it follows that the diagnosis of a mitral insufficiency should never be made from auscultatory findings alone Only those who follow this rule will avoid errors of serious consequence *In the presence of a systolic apical murmur mitral regurgitation should be diagnosed only if the left atrium and ventricle are enlarged*

Left Atrium and Ventricle Whereas in mitral stenosis dilatation of the left atrium may be absent for a long time this dilatation occurs early in mitral regurgitation In mitral stenosis the left atrium may overcome the obstruction by means of hypertrophy alone at least for some time In this lesion the atrium dilates secondarily if compensation by simple hypertrophy is impossible On the other hand in mitral insufficiency the left atrium dilates from the beginning (primarily) because with valvular incompetence the left atrium fills from both sides backwards and under high pressure from the ventricle as well as normally from the pulmonary veins The dilatation of the left atrium may be enormous the term aneurysm has sometimes been applied to it

Parallel and coincidental to the atrial dilatation the left ventricle also dilates since in a pure insufficiency the patent mitral orifice permits the left ventricle to overfill in diastole (figure 34)

If enlargement of the left atrium and ventricle cannot be demonstrated by percussion fluoroscopic examination becomes necessary to confirm the diagnosis The finding of an esophageal displacement in the right anterior oblique position is often decisive for the diagnosis If no abnormality is revealed by this examination it is well to re examine the patient after a few months The diagnosis of a mitral insufficiency may be discarded if the left atrium remains normal A normal left atrium and left ventricle are found only in patients with negligible mitral insufficiency

Electrocardiography

This gives no assistance in the diagnosis of a mitral insufficiency With hypertrophy and dilatation of the right and left ventricle there is often no axis deviation

Catheterization and Diagnosis During Surgery

When during cardiac catheterization the tip of the catheter is wedged into a small pulmonary artery and the pressure registered it is claimed that a large systolic pulse wave appears in the presence of mitral regurgitation This sign however proved unreliable With a finger in the left atrium the surgeon can readily feel the regurgitating jet and — from its strength — can draw a conclusion as to the degree of regurgitation With this method mitral insufficiencies were discovered when no systolic murmur existed at the apex on the other hand as pointed out before loud systolic murmurs have been found with no evidence of mitral regurgitation a lesion of a different degree than the clinician had concluded from the loudness of the murmur may be found

Other Diagnostic Methods In pure or predominating mitral insufficiency there is no opening snap and no accentuation of the first apical sound Gallop rhythm occurs Systolic expansion of the left atrium can be seen fluoroscopically but often is missed these expansions have been registered in the esophagogram fluorocardiogram and kymogram All these methods of examination contribute very little If in a proven mitral stenosis roentgen examination particularly

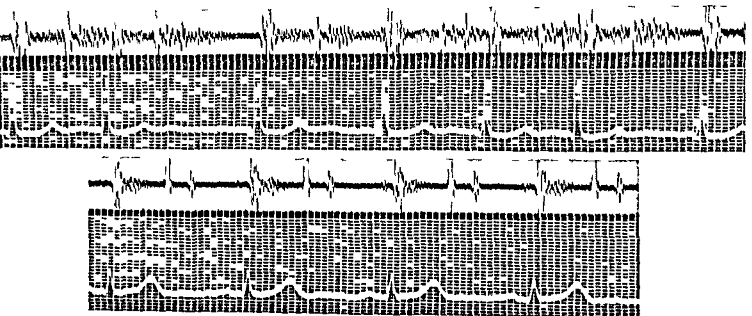


Fig 35 (a) Obtained at the apical area from a 54 year old woman with mitral regurgitation and stenosis and atrial fibrillation a blowing systolic and a rumbling diastolic murmur were heard (b) Obtained from a 22 year old woman with rheumatic mitral regurgitation the tracing was obtained at the cardiac apex and shows a systolic murmur and gallop rhythm

in the left oblique position reveals an enlargement of the left ventricle there is a strong probability in favor of a mitral insufficiency but an aortic lesion must also be ruled out In the latter the aortic knob is well developed while it is usually missing in pure mitral lesions

Differential Diagnosis

The outstanding problem in differential diagnosis of a mitral insufficiency is the distinction of the systolic apical murmur from a physiologic murmur (This was discussed in the preceding pages) The differentiation between an organic and a relative mitral insufficiency (which was often called functional) is easy if there is a diastolic murmur indicative of mitral stenosis (figure 35) This can only mean a rheumatic etiology If however the systolic apical murmur alone is found and the heart displays a mitral configuration relative as well as organic mitral insufficiency may be present Gallop rhythm (figure 36) occurs in both forms of mitral regurgitation If the signs of the valvular lesion disappear during treatment one may properly assume the existence of a relative mitral insufficiency which disappeared when the state of the heart muscle improved Otherwise only careful investigation and the demonstration of some disease which might lead to marked dilatation of the left ventricle and a relative insufficiency of the valve permit one to reach a differential diagnosis Occasionally the history will assist A patient with a rheumatic lesion of the mitral valve complains of increasing exertional dyspnea A patient with relative mitral insufficiency presents typical paroxysmal nocturnal dyspnea characteristic of left ventricular failure

It should be kept in mind that relative mitral insufficiency is a complication of some heart lesion and is not an entity sui generis

Prognosis

Statements concerning the outlook for a patient with mitral insufficiency should be guarded In older reports the prospect was often described as excellent This is understandable because rather often the diagnosis was made in healthy individuals with a physiologic murmur If the diagnosis however is limited to real cases of mitral insufficiency it is soon discovered that patients with mitral insufficiency or a double mitral lesion with a predominating insufficiency develop *the picture of complete and irreversible decompensation* in a relatively short time This is partly due to the early and sometimes enormous dilatation of the left atrium and ventricle

The combination of mitral insufficiency with stenosis has its favorable aspects the stenosis prevents overfilling and dilatation of the left ventricle even when the left atrium is markedly distended

Surgical Therapy This is still in the experimental stage and it is too early for a proper evaluation Venous and pericardial grafts have been used in dogs Mitral suturing has been attempted With deformities of the valves mitral commissurotomy may decrease the degree of regurgitation but often results in an increase

TRICUSPID REGURGITATION

This lesion is still frequently overlooked by physicians who rely largely on auscultation for the diagnosis of valvular lesions The diagnosis however, is often readily made by other methods

Etiology

Isolated rheumatic involvement of the tricuspid valves is extremely rare A combination of rheumatic valvulitis of the mitral aortic valves and evidence of a similar process in the tricuspid valves is common Various statistics indicate that careful examination will disclose tricuspid valve involvement in 20 to 30 per cent of the patients with rheumatic mitral disease

There are rare instances of an isolated tricuspid insufficiency resulting from healed bacterial endocarditis

A relative tricuspid insufficiency due to dilatation of the right ventricle is the type most often encountered It may be present with a moderate dilatation of the right ventricle or absent when there is considerable dilatation It is commonly associated with rheumatic mitral lesions which lead to an enlargement of the right ventricle and with myocardial diseases of various etiologies One case of a relative tricuspid and mitral insufficiency developing in the course of intractable paroxysmal ventricular tachycardia which lasted for years has been described elsewhere (Scherf and Kisch)

Congenital tricuspid insufficiency due to malformation of the valve is also known (Barritt and Urich)

Dynamics

If the tricuspid valves are incapable of closure a certain amount of blood is sent back into the right atrium during systole Right atrial dilatation develops early and is accompanied from the beginning by dilatation of the right ventricle In an uncomplicated case the regurgitating blood fills the right atrium without creating any abnormal sign If congestion increases however or if the atria fibrillate regurgitation even of small quantities of blood provokes certain easily detected signs

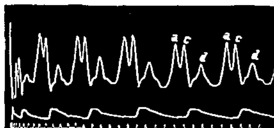
In an advanced tricuspid insufficiency the left ventricle is said to undergo atrophy due to inadequate filling

Symptoms

It is characteristic for patients with tricuspid regurgitation to have but few complaints There is no dyspnea unless physical exertion exceeds certain modest limits No orthopnea or paroxysmal nocturnal dyspnea are observed Sleep is undisturbed Digitalis in remarkably small amounts and above all diuretics keep these patients well for a long time

Signs

Positive Venous Pulse The diagnosis is often possible by inspection In healthy people a venous pulsation composed of three waves can often be observed in the neck veins Figure 36 a shows a normal venous pulse The first wave (the a wave) arises during and in connection with atrial systole while the c wave and v wave arise *during ventricular systole During a large part of ventricular* systole blood is expelled into the peripheral arteries thus increasing the negative *pressure within the chest this facilitates the inflow of blood into the chest so*



a



b

FIG 36 (a) Normal venous pulse (b) A positive venous pulse in a patient with tricuspid regurgitation and atrial fibrillation the fibrillation waves are visible in the venous pulse

that the neck veins are not engorged Accordingly there is a deep collapse between the c and v (or d) waves The normal physiologic venous pulse is called negative because of this depression during a good part of systole

With marked congestion and particularly when atrial fibrillation co exists the systolic collapse in the venous pulse may become less distinct or may disappear entirely without a tricuspid insufficiency being present The reason for this is as follows ventricular systole has little or no effect on the venous blood flow in advanced stages of congestion the veins remain constantly distended and may show no pulsations at all This can be demonstrated even in beginning right heart failure by pressure on the right upper abdomen Such pressure increases the return of blood to the right heart and distends the veins to a greater extent and for a longer time than under normal conditions and abolishes pul sations of the vein

In tricuspid insufficiency the systolic regurgitation of blood into the right atrium may cause the transmission of a pulsation into the neck veins, a finding that becomes increasingly obvious if the atrium and the veins are overfilled due to congestion The collapse between the c and v waves disappears both waves merge into a single large one and the venous pulse is 'positive Figure 36b shows a positive venous pulse from a patient with tricuspid insufficiency Atrial fibrillation is also present in this patient and therefore the a waves are abolished

In tricuspid insufficiency the back flow of blood under the high pressure created by ventricular systole causes a visible pulsation in the neck If the jugular veins are compressed halfway along their course this pulsation is still visible below the point of compression This shows that a real backflow from the heart is responsible

The pulsations are often absent from the superficial neck veins for these vessels are so distended that they cannot pulsate The vein in which the pulsations are distinct is the deep jugular vein which is covered by the sternocleidomastoid muscle As the result of persistent regurgitation of blood under ventricular pressure the vein wall distends Often the internal jugular vein is so wide that at necropsy three fingers can easily be introduced into the lumen without stretching it In such cases a broad pulse wave ascends the neck with each systole and lifts the sternocleidomastoid muscle It ascends up to the lobe of the ear Students often confuse these strong pulsations with the Corrigan pulse of aortic insufficiency For differentiation one can easily discover that peripheral arteries do not show a collapsible pulse while palpation of the pulsating vessels reveals the low venous pressure Furthermore the pulsation is not jerky but ascends relatively slowly

The pulsations are usually most distinct on the right side for the right innominate vein ascends in direct continuity whereas the left departs from the superior vena cava at approximately a right angle In rare cases we have seen a stronger pulsation on the left presumably the result of an anatomic anomaly in these vessels

With marked venous stasis the pulsations may be visible only when the patient is erect in this position the pressure within the neck veins diminishes somewhat as the inflow of blood into the right atrium improves This leads to less distention of the vessel and permits pulsations to appear Often venous pulsations are absent in all positions but reappear as soon as successful treatment lowers the venous pressure In early cases the huge right atrium can accept regurgitating blood and no abnormal venous pulse is noted in the neck In these cases the characteristic pulsations appear only in the recumbent position or if the amount of blood flowing back to the right heart is increased by compression of the right upper abdomen

Some patients are profoundly distressed by the regurgitation of blood into the neck veins at least when this first happens They suffer from throbbing in the ears probably owing to the impact of the regurgitating blood on the bones enclosing the veins in the head the pulsations are regular with sinus rhythm

and irregular in fibrillation The patient can readily count the heart rate by the throbbing alone This sensation is aggravated by certain positions of the head and is diminished in others A general oppression is felt in the neck as the result of increased systolic filling of all deep veins

Positive Liver Pulse The blood driven back into the right atrium by venticular systole does more than reach the tributaries of the superior vena cava It also flows back into the domain of the inferior vena cava particularly through the wide open valveless hepatic veins A systolic swelling of the liver a systolic liver pulsation is the result

Systolic pulsations of the liver occasionally occur without tricuspid insufficiency Massive right ventricular hypertrophy may thrust the liver downward when the impact of cardiac systole is transmitted through the diaphragm The abdominal aorta may push the liver ventrad in the midline Like other organs the liver may show systolic pulsations if there is an aortic regurgitation and the hepatic arteries pulsate strongly Local systolic pulsations may occur in the neighborhood of a liver abscess

The hepatic pulsation of tricuspid insufficiency can be differentiated from the above mentioned forms for it is expansile The liver volume increases in all directions a fact easily discovered if both hands are applied at some distance from each other By this means the systolic increase of the liver volume is readily distinguished from a transmitted cardiac or aortic pulsation In early cases the pulsation is absent since the pressure of regurgitating blood is not sufficiently high to distend the liver We have seen it disappear during the course of the disease when the amount of fibrotic tissue in the liver increased and cirrhosis developed The enlarged liver is not tender unless congestion develops acutely or is of recent origin

At times systolic pulsations may be noted in other regions such as the spleen or the peripheral veins Pulsations of the veins of the forearm and of other peripheral vessels occur but with less regularity and less characteristically than the positive venous and hepatic pulse The venous pulsations in the arms may be demonstrated by raising the arm almost to the level at which the veins collapse

Pulsations of the Chest Marked liver pulsation causes a distinctly perceptible movement of the right upper abdomen to the right The hypertrophy and dilatation of the right ventricle simultaneously displace the thorax to the left so that a characteristic see saw movement is visible

Inspection reveals the systolic retraction of the interspaces over the precordium which is typical for right ventricular hypertrophy and dilatation and there is a strong diastolic bulging

Ascites Edema The great stasis created in the portal circulation by the systolic regurgitation of blood into the liver produces ascites another sign characteristic of a fully developed tricuspid insufficiency It is rarely absent In many cases ascites is the outstanding feature and requires the continuous administration of mercurial diuretics At present in many cases paracentesis

can be avoided or postponed for years by the skillful employment of these compounds In the course of time more or less evidence of cardiac cirrhosis may appear

Edema is common in relative tricuspid insufficiency and anasarca is not rare The edema may vanish while the ascites persists The appearance of edema may coincide with effusions into the serous cavities

Cyanosis Despite enormous dilatation of the right heart cyanosis is often absent It has been pointed out earlier that with the appearance of right ventricular failure and the development of hepatic congestion cyanosis if previously present may vanish If right heart failure develops acutely the patient may even show marked pallor owing to the retention of quantities of blood in the liver and veins In accordance with these events x ray examination discloses relatively clear lung fields in tricuspid insufficiency

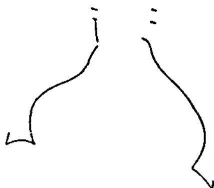


FIG 37 Typical orthodiagram from a patient with tricuspid regurgitation

Percussion and X ray Examination This provides evidence of dilatation of the right atrium and ventricle These findings are not characteristic because they appear regularly in certain stages of the underlying accompanying condition (rheumatic mitral lesion or myocardial disease)

The dilatation of the right atrium however may reach considerable dimensions (figure 37) The vascular band widens owing to the congestion of veins near the heart

Auscultation The systolic murmur one might expect to hear at the lower end of the sternum at the site of auscultation of the tricuspid valve is absent in most cases While the mute variety is exceptional in other valvular lesions it is the rule in tricuspid insufficiency Contrary to statements by many authors in a large series of patients with tricuspid insufficiency with the diagnosis confirmed at necropsy we gained the impression that a distinct murmur over the tricuspid area is an exceptional finding To be sure systolic murmurs are often detected in this area however one cannot be certain that they are not transmitted from the mitral or pulmonic valve Although a murmur heard over the tricuspid area may sound different at this point from one at the mitral area this does not mean there are two different murmurs The characteristics of a murmur may be changed more or less through transmission because the tissues filter it

The reason for the frequent absence of a separate systolic murmur over the tricuspid area in tricuspid insufficiency is not known The valve is not situated deeply and conditions for transmission to the surface of the thorax are good In many cases it seems that the murmur is conducted better to the apex and is

then confused with a mitral murmur This mistake is more apt to occur in those cases where the heart rotates to the left when the right ventricle dilates

The statements in the preceding paragraphs disagree with those of many authors (Muller and Shillingford) who found a murmur in the fourth intercostal space to the left of the sternum to be the earliest and best sign of tricuspid incompetence

The second pulmonic sound is rarely accentuated The signs of aortic incompetency may disappear when a tricuspid regurgitation develops

Differential Diagnosis

Differentiation between a relative and an organic tricuspid insufficiency is not possible as a rule on the basis of the clinical findings Even if evidence of tricuspid regurgitation appears during decompensation it is possible that regurgitation was present before but evoked no signs to permit the diagnosis In a similar way the disappearance of signs of tricuspid regurgitation during successful treatment may be due simply to diminished congestion and does not necessarily signify that a relative tricuspid insufficiency has disappeared It has been claimed that in tricuspid lesions caused by valvular disease the systolic venous wave appears later and reaches its peak later than in relative tricuspid insufficiency Only in a pure myocardial lesion may one assume that the signs of tricuspid insufficiency appearing during decompensation are due to a relative insufficiency

Cardiac catheterization reveals a higher diastolic atrial pressure compared to that in the right ventricle (Whitaker)

Prognosis

The frequently expressed opinion that the appearance of a tricuspid regurgitation signifies a serious complication of bad prognostic significance cannot be accepted without reservation Patients with an organic (more rarely with a relative) tricuspid insufficiency have been under our observation for more than eight years and have remained in a tolerable condition The greatest danger to which these patients are exposed is pulmonary embolism

The safety valve function of a tricuspid regurgitation in relieving the pressure in the lesser circuit was described as early as 1837 by King

TRICUSPID STENOSIS

Etiology

This lesion is an occasional sequela of a rheumatic involvement of the tricuspid valves and under these circumstances always accompanies a rheumatic mitral and/or aortic lesion It is much more common in women than in men In rare cases congenital tricuspid stenosis is produced by a malformation in this variety other malformations particularly atrial septal defects are usually present The tricuspid stenosis in metastasizing carcinoids will be discussed later

Symptoms and Signs

There are no characteristic symptoms or signs The diagnosis is made only on the basis of a syndrome that is not entirely typical and that hardly amounts to more than a suspicion

Patients with tricuspid stenosis are usually cyanotic and have a definite yellow complexion (subicterus) The right atrium is very large The neck veins are congested and show presystolic pulsation (an accentuated a wave) The presystolic venous (and liver) pulse can be registered by graphic methods they are not pathognomonic for they may be noted in other conditions e g pericardial adhesions One may palpate a bifid liver pulsation Clubbing of the fingers is common and a polycythemia is often noted The peripheral pulses are small

On percussion and x ray examination the heart shows a pronounced dilatation to the right since the right atrium enlarges The vascular band at the base of the heart is wide owing to dilatation of the veins The lung fields are clear there is no pulmonary congestion

Auscultation usually reveals no abnormality Sinus rhythm is common In some exceptional cases rumbling diastolic murmurs are said to be audible at the lower left sternal border We have never found them despite the observation of a number of cases verified at necropsy

An opening snap is heard over the tricuspid area or to the right of it it appears about 0 1 second after the onset of the second sound (Kossmann)

The liver is markedly enlarged and ascites is frequently found All these signs depend upon the fact that the right atrium is unable to empty its contents normally into the right ventricle and therefore some blood returns to the veins during atrial contraction (in presystole) Sometimes the right ventricle is smaller than normal just as the left ventricle is atrophic in mitral stenosis Large P waves are seen in the electrocardiogram

Catheterization may reveal a higher mean pressure in the right atrium The resting cardiac output is reduced (Ferrer et al)

Diagnosis

If there is pronounced dilatation of the right atrium and massive congestion of the liver in a patient with rheumatic mitral or aortic valvular disease without evidence of tricuspid insufficiency or pericardial adhesions and if the patient shows cyanosis and some jaundice the presumptive diagnosis of tricuspid stenosis is justified If there is no fibrillation the presence of presystolic pulsations of the jugular veins and of the liver gives some support to this diagnosis The diagnosis is also probable but unproven when an expansile liver and positive venous pulse gradually diminish in a tricuspid insufficiency despite increasing cardiac dilatation and decompensation In this case one may justifiably assume the existence of a tricuspid lesion in which an increasing stenosis progressively displaced the signs of insufficiency

Pulmonic Regurgitation

Etiology

Rheumatic involvement of the pulmonic valve is exceedingly rare Occasionally bacterial endocarditis causes pulmonary regurgitation and even more rarely the endocarditis heals leaving the patient with a pure valvular insufficiency We have had the opportunity to observe only one case of this type but they will doubtless be seen more often since the introduction of the modern antibiotic treatment of bacterial endocarditis Congenital pulmonary insufficiency is likewise rare in such cases the number of cusps of the pulmonic valve is usually increased or decreased

Relative insufficiency of the pulmonic valve is much more common It seems to affect both sexes equally and to occur at all ages although the vast majority of cases are discovered in adult life In a majority of these cases a rheumatic mitral stenosis coexists If pressure is high in the lesser circuit as indicated by an accentuation of the second pulmonic sound and a wide pulmonary artery a soft diastolic murmur may appear in the second or third interspace to the left of the sternum (Graham Steell murmur) It has the same pitch and the same site as the murmur of aortic insufficiency It may be temporarily louder then vanish to reappear from time to time If insufficiency of the aortic valve has been diagnosed one is surprised to find these valves normal at necropsy

The murmur has been designated as the murmur of high pressure A considerable increase of pressure in the lesser circuit may produce such marked dilatation of the pulmonary artery and valvular ring that the valves — otherwise normal — are unable to close

If one has the opportunity to observe a large number of patients with mitral stenosis over a period of years relative pulmonary insufficiency is not rare Cabot observed it in 22 of 55 autopsied cases of mitral stenosis It disappears if pressure in the lesser circuit falls as the right heart fails or a relative tricuspid regurgitation develops it reappears if the former status is restored by treatment

The comparatively frequent occurrence of relative pulmonary insufficiency in mitral stenosis requires an explanation for it stands in striking contrast to the rarity of relative insufficiency of the aortic valve Undoubtedly one reason is found in the local anatomy The root of the pulmonary artery and the valvular ring is weaker than that of the aorta Another factor is the preference of rheumatic histologic changes to involve the conus of the pulmonary artery and the root of the artery itself Accordingly weakness or destruction of these structures makes the appearance of a relative pulmonic regurgitation easier if pressure rises in the lesser circuit

Relative insufficiency of the pulmonic valve also develops in other conditions which increase pressure in the lesser circuit e g in fibroid tuberculosis extensive myocardial lesions and kyphoscoliosis

There are no characteristic symptoms

Signs

Invariably the second pulmonic sound is palpable and markedly accentuated in these cases unless emphysema coexists The conus of the pulmonary artery and the pulmonary artery itself are dilated Since the right heart enlarges markedly a very characteristic configuration pouter heart appears Figure 38 shows the orthodiagram obtained from a rheumatic mitral stenosis and relative pulmonary incompetency showing the characteristic change of cardiac shape

According to Hall a diastolic thrill occurs only in the organic and never in the relative insufficiency of the pulmonic valve It has been found however in a case of relative pulmonic insufficiency that was examined at necropsy This should be expected because the intensity and pitch of the murmur rather than the etiology is decisive for the presence or absence of a thrill



FIG 38 Typical orthodiagram from a patient with rheumatic mitral stenosis and relative pulmonary insufficiency (pouter heart)

A loud systolic murmur over the pulmonary artery is heard in all cases It is explained by the dilatation of the pulmonary artery and the right ventricle (relative stenosis of the ostium)

On fluoroscopy a pulsus celer of the hilar vessels gives a very characteristic picture although it is not always present Hilar dance is not pathognomonic for it occurs in many condition as mentioned in the preceding chapters The lung fields are relatively clear since the relative pulmonary insufficiency acts like a safety valve for the lesser circuit and diminishes congestion Dilatation of the pulmonary artery occurring in mitral stenosis without relative pulmonic regurgitation is not typical

Differential Diagnosis

Relative pulmonic regurgitation is most often confused with rheumatic aortic insufficiency because the location and type of the murmur is the same for both lesions Therefore it should be strongly emphasized that auscultatory findings alone are not the basis for diagnosis All physical signs and the results of fluoroscopy must be evaluated The absence of peripheral signs of aortic insufficiency should not be used against the diagnosis of this lesion for a coexisting mitral stenosis may abolish the peripheral and even the auscultatory signs of aortic valve involvement

The correct diagnosis may also be difficult when there is a silent mitral stenosis Often a positive diagnosis must await necropsy

The prognosis depends upon the underlying lesion

Pulmonary Stenosis

Since pulmonary stenosis is ordinarily a congenital heart lesion and is often associated with other malformations discussion of its symptomatology will be deferred This seems particularly advisable since the symptoms signs and prognosis depend to a vast extent upon the associated conditions The pulmonary stenosis in carcinoids is discussed below

Combined Lesions of More than One Valve

The essential features of most combined valvular lesions have been mentioned in the preceding pages In a large majority the mitral lesions constitute the fundamental disturbance The prognosis depends not upon the number of valves involved but almost invariably upon the status of the myocardium

Mitral aortic and tricuspid lesions represent a common combination Under this circumstance the tricuspid lesion may be organic or relative These patients may remain in relatively good health for years despite the existence of a cor bovinum

Since diastolic murmurs may be absent in such combined lesions and non characteristic systolic murmurs alone may be present it may be difficult to decide whether a rheumatic trivalvular lesion exists or simply a decompensated heart from a myocardial disturbance or hypertension with relative mitral and tricuspid insufficiency

It must be stressed again that the systolic murmur of aortic stenosis may be louder at the apex than over the aortic area while the diastolic murmur of aortic regurgitation may be absent over the aortic area but may be very loud over the left lower sternal border

Sometimes only the presence of a pulsus celer of the aortic knob will indicate the presence of an aortic insufficiency in mitral lesions on fluoroscopy

For the diagnosis of a silent mitral stenosis in combined lesions no sign is of greater value than the accentuation of the first heart sound with the snappy apex beat

Often x ray examination and electrocardiography offer some assistance in the differential diagnosis of combined lesions The presence of widened and notched P waves in leads I and II will speak in favor of the presence of a rheumatic mitral stenosis The advantage or disadvantage of the different combinations of single valvular lesions has often been discussed Conclusions reached on this subject as a rule are merely speculative

Carcinoids and Valvular Lesions of the Right Side of the Heart

Recently a well defined and readily recognizable syndrome has been observed in connection with carcinoids of the small intestine with metastases (argentaffinoma) (Isler and Hedinger)

Among other interesting features the patients suddenly develop flushes and report rapid changes in the color of the skin (deep red or purple) particularly

induced by emotions or physical exertion sometimes permanently Cyanotic or white patches are temporarily visible Telangiectasias are common Watery diarrhea (up to 30 stools daily) and abdominal pains may occur along with right heart failure with edema and ascites, more rarely attacks of asthma appear

An intestinal carcinoid with metastases to the liver is regularly found The pulmonary and tricuspid valves become thick and stenotic or insufficient the valves of the left heart remain normal usually but may also be involved (McKusick) Marked thickening and swelling of the endothelium of the hepatic veins has been found (Hegglin and Zollger)

The secretion of a vasoactive hormone by the carcinoid tissue has been known for many years The carcinoid produces a substance called serotonin (Lembeck Thorson et al) which is under extensive investigation This compound 5 hydroxytryptamine which is vasoactive and may lead to an elevation of pulmonary blood pressure and bronchial constriction seems necessary for normal mental processes (Wolley) It is found in the blood platelets and can be easily recovered from clotted blood It is found physiologically in the intestinal mucosa produced by the argentophile cells and is therefore called enteramine (Erspamer) The platelets absorb it The substance seems to be inactivated to a great extent in the lungs so that the left heart is usually spared (Gobel et al) The valve lesions are not explained One is reminded of the valvular changes observed by Lillehei in arteriovenous fistulas A color test has been developed to detect the excretion of metabolites of serotonin (5 hydroxy indole acetic acid) in the urine (Hanson and Serin Sjoerdsma et al)

Thickening and fibrosis of the endocardium involves also the chordae tendineae and the wall of the ventricles it does not concern the valves exclusively

A high incidence of congenital cardiovascular anomalies has been reported in these cases (Spain)

Therapy is limited so far only to reducing the size of the tumor

Even after metastases occur the disease may last up to 20 years (Ritchie)

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Chapter 13

Diseases of the Myocardium

INTRODUCTION

THE TERM "MYOCARDIAL DISEASE" is applied to a heterogenous group of affections and includes, by common consent, primary lesions of the myocardium, secondary involvement of the muscle in the course of various diseases, as well as the myocardial damage associated with coronary artery disease. The great significance of myocardial lesions in national health is obvious from their incidence.

Students and young physicians who attend lectures and postgraduate courses often gain a false impression of the incidence and importance of myocardial disorders because valvular lesions with their richer symptomatology and abundance of demonstrable signs are presented much more often than the less colorful myocardial diseases. In practice, however, the diseases about to be discussed are much more common.

In these conditions more than anywhere else in cardiac patients a careful history and percussion are of paramount importance for the bedside diagnosis in many cases. Without percussion, a severely affected myocardium may seem normal to many physicians, *particularly when murmurs are absent*. Very often these patients present no signs that are easily detected by auscultation; therefore, physicians who rely on murmurs for the diagnosis of heart lesions, without such laboratory aids as the x-ray or the electrocardiogram, will often overlook a serious cardiac affection. Unfortunately, a considerable number of doctors learn the clinical aspects of the diseases now to be discussed only after they have gained experience by serious mistakes.

For a long time all myocardial diseases have been lumped together in one category. Every cardiac lesion not caused by valvular involvement was regarded as the result of "myocardial degeneration." This was followed by an era of "myocarditis," when elaborate classifications of parenchymatous and interstitial myocarditis were developed. For a time practically all myocardial lesions were discussed under this heading. Monographs on "myocarditis" were written and oddly enough made no mention of myocardial inflammation (which alone, obviously, is myocarditis). Actually the lesions secondary to coronary sclerosis were exclusively described. Ultimately there was a natural reaction to this unwarranted emphasis upon myocarditis, and textbooks on cardiovascular diseases were written which did not even mention this lesion. A more objective attitude is encountered at the present time.

There are not many other subjects in cardiology which have undergone greater change in recent times With the advance in knowledge the clinical diagnosis has become possible in many cases

MYOCARDITIS

Incidence

As in the earlier editions of this book we wish to stress at the outset that myocarditis is a common disease and that the attitude still prevailing in many quarters where myocarditis is regarded as uncommon is unjustified and incompatible with present knowledge Adequate data have accumulated to show that neither the incidence nor importance of this disease was correctly appraised in the past

Histologic examination of the heart in over 5000 necropsies on adults who died from other than a contagious disease revealed myocarditis in 4 26 per cent The percentage was even higher in children i e 6 83 per cent (Saphir)

Pathology

Grossly the soft flabby yellow or brown muscle resembles the pallid heart seen in connection with marked cloudy swelling Microscopically nonsuppurative myocarditis shows granular and hyaline necrosis in small foci surrounded by interstitial collections of cells The infiltrate is composed chiefly of lymphocytes polymorphonuclear leukocytes and plasma cells at times large numbers of eosinophiles are encountered The amount of inflammatory edema varies and small hemorrhages may be observed

In some coccal infections (strepto staphylo pneumo and gonococcal) small multiple abscesses may form particularly in the left ventricle The histologic picture is that of a focal abscess surrounded by a dense cellular infiltrate Early death from the provocative sepsis may preclude the detection of reparative processes

Common Varieties

Myocarditis may accompany local or general infectious diseases and it may be essential that is without apparent involvement of other organs Among the more important diseases in which myocarditis is known to occur the following must be mentioned

Rheumatic Fever It is universally agreed that myocarditis is extremely common in the acute phase of rheumatic fever some observers even consider it a constant phenomenon This conclusion is based largely upon histologic and electrocardiographic studies

The many cases of rheumatic myocardial damage the appearance of Aschoff bodies round cell infiltrations and changes in the coronary arteries leading to the occlusion of small vessels have been discussed earlier Occasionally symptoms or signs of rheumatic myocarditis lead to the diagnosis of active rheumatic fever

which earlier was unrecognized This lesion has been discussed in the chapter on rheumatic fever

Tonsillitis Not rarely tonsillitis as well as other infections of the throat provoked by hemolytic streptococci cause an acute myocarditis In some cases *evidence of cardiac participation is obtainable one or two days after the onset of* tonsillitis more frequently it appears 6 to 8 days after the throat infection starts Often the changes are not detected until the fever has subsided There is no parallelism between the severity of the tonsillitis or sore throat and the myocardial changes Occasionally a severe myocarditis develops in patients who have had only a few hours of fever sometimes they have not felt sufficiently ill to go to bed or else the tonsillitis was subclinical

Opinions are still divided on the incidence of myocarditis following tonsillitis According to some observers evidence of myocarditis is obtained electrocardiographically in 70 per cent of the cases This figure is certainly too high Marked changes consisting of widening of the QRS complexes to more than 0 10 second prolongation of the P—R interval abnormal RS T segment and abnormal T waves appeared in 30 per cent of another series (Hotz and Huber) According to personal experience 10 to 15 per cent of patients suffering from an acute tonsillitis develop changes suggestive of myocardial involvement

The patients complain of weakness palpitation and cardiac pain The pain may appear suddenly and without apparent provocation such as exertion it is felt behind the sternum or over the precordium it may radiate like the typical anginal pain to the right or left shoulder and arm Sometimes the distress is mild and is revealed only when the patient is specifically interrogated about it in other cases it is excruciating The pain may last only a few seconds rarely it persists for minutes and it recurs often

The signs are the same as those of other types of myocarditis and will be discussed later in this chapter

Often the lesion is overlooked The weakness and palpitation are attributed to the preceding infection or to the absorption of toxins Little attention is paid to the pain when it is atypical the patient is often young and therefore anginal pain is out of the question

The alterations in the electrocardiogram provide the best objective evidence of cardiac participation Temporary prolongation of the atrioventricular conduction time and periodically dropped beats (Wenckebach periods) may appear T wave changes are common These changes usually disappear in a few days rarely are they demonstrable for four to six weeks In some cases the conduction time remains prolonged even after full recovery takes place

Within the space of a few months the wives of two hospital administrators in the same institution complained of palpitation general weakness and cardiac pain following mild tonsillitis One patient had a temporary prolongation of the A V conduction time to 0 23 second and the other to 0 32 second Both women were young and otherwise healthy no subsequent evidence of rheumatic fever could be obtained and complete recovery was noted within two weeks

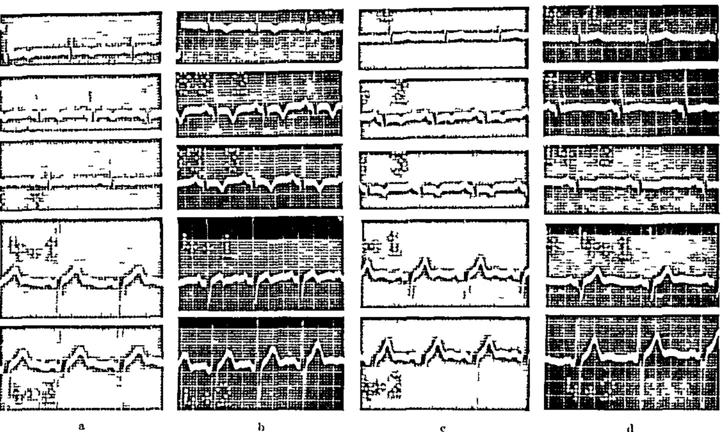


Fig 39 A series of tracings from a patient with myocarditis following tonsillitis The three standard leads are followed by CR4 and CR2

Figure 39 was obtained from a 25 year old man who came to the hospital with a severe tonsillitis and pharyngitis his temperature was 40° C Weakness and palpitation were the chief complaints Physical examination disclosed nothing abnormal except for the throat involvement Within five days the fever and tonsillitis subsided under sulphonamide therapy but the weakness and palpitation persisted for several weeks

The first electrocardiogram (figure 39 a) was taken on the second day of hospitalization The T waves are inverted in leads I and II The second electrocardiogram was recorded 6 days later one day after the fever disappeared It shows a sinus tachycardia of 100 and deeply inverted T waves in each limb lead The third tracing (figure 39 c) was obtained three weeks after the preceding and shows evidence of improvement The fourth tracing (figure 39 d) was obtained 18 days after the third and is almost normal The patient remained under observation and at no time presented evidence of rheumatic fever

Usually the prognosis is good because signs of cardiac involvement disappear within a few days or weeks We have never seen acute heart failure develop It is possible however that patients who are unaware of the existing condition may undertake severe exertion during the acute stage of myocardial involvement under these circumstances cardiac dilatation and congestive heart failure might develop Embolism of the systemic arteries may arise from mural cardiac thrombi but fortunately this is a rare event Little is known about any permanent weakness of the heart muscle due to scar formation following myocarditis (myocardial fibrosis)

The differential diagnosis is not always simple The process must be distinguished from rheumatic fever This is often difficult in view of the fact that arthralgias occur occasionally in connection with streptococcal infections of the upper respiratory tract Under these circumstances the sedimentation rate is of great help since it shows abnormal values for a long time in rheumatic fever but only a slight change for a few days after a streptococcal pharyngitis or tonsillitis Sometimes however differentiation of the two conditions is impossible in the beginning There is certainly an interrelation although the connections are understood only in part at present

Relatively little is known about the myocardial pathology since it is exceptional for these patients to succumb in the acute stage when a histologic study would be informative Available evidence however justifies the term myocarditis for the cardiac lesions It is of importance that most of the patients who succumbed to a simple streptococcic throat infection also had hyperthyroidism In a patient with mild hyperthyroidism who developed a complete heart block following tonsillitis an inflammatory lesion in the heart muscle particularly in the bundle of His contained gram positive bacteria (Davis and Smith) In experimental streptococcus infections in the rabbit inflammatory foci were seen in the myocardium for the most part around the small branches of the coronary arteries Therefore the possibility of an allergic response similar to that in rheumatic fever seems eliminated (Weicker and Petzlaff)

Penicillin should be given immediately 600 000 to 1 200 000 units being administered daily for several days Tonsillectomy should not be performed until six weeks after all signs of activity have disappeared Rest in bed is essential this must be enforced for days weeks or months in accordance with the clinical and electrocardiographic signs

Other Focal Infections These may likewise be accompanied by myocarditis Dental infections with or without focal abscesses or a tonsillar abscess are rarer causes of myocarditis than was formerly believed but such cases undoubtedly occur

An 18 year old man was admitted complaining of dyspnea and palpitation The heart was moderately enlarged and the sounds were pure A secondary anemia was present and the temperature underwent an occasional slight rise The electrocardiogram was repeatedly found normal until one examination disclosed a prolongation of the A V conduction time A renewed search for a focus of infection revealed a large latent apical abscess of one devitalized tooth Extraction of the offending tooth led to rapid and complete recovery of the patient

It is claimed that colitis cholecystitis adnexitis accessory sinus infections pyelitis and prostatitis may also act as foci and initiate a myocarditis in rare cases

Scarlet Fever Myocarditis is common in this disease Electrocardiographic alterations were found in 20 to 25 per cent of the cases observed Inflammatory changes likewise occur particularly around the small branches of the coronary arteries Histologic studies in scarlet fever and related streptococcal infections disclose focal and diffuse interstitial infiltrations in the myocardium in 90 per cent of the cases According to some authors rheumatic fever is superimposed in these cases whenever there are definite clinical signs of myocardial involvement

Coccal Infections Systemic diseases caused by staphylococci gonococci and meningococci often cause acute myocarditis as well as endo and pericarditis Modern treatment with the antibiotics permits a larger number of patients with these infections to survive and therefore more cases of myocarditis (and pericarditis) caused by these bacterial agents are observed

Parasites In trichiniasis the heart muscle is often involved and electro cardiographic changes are common They disappear soon and the parasite vanishes if the patient survives Focal myocarditis has been seen in toxoplasmosis (Paulley et al)

Syphilis Myocarditis is certainly rare in syphilis While it has been claimed that syphilis causes a diffuse chronic myocarditis and perhaps sudden death increasing doubt has been raised concerning the criteria for an anatomic diagnosis Spirochetes may abound in the myocardium of stillborn infants but inflammatory reactions are absent The importance of syphilis in the causation of coronary ostial stenosis and the resultant train of symptoms will be discussed later

Trypanosomiasis Chagas disease is known to cause myocardial lesions and cardiac arrhythmias Its high frequency in certain parts of South America has

been recognized lately (Rosenbaum and Mora) This disease may in the future assume importance in the United States

Tuberculosis Myocarditis although a common event in tuberculosis often is not evaluated correctly In our experience electrocardiographic changes are frequent in active exudative pulmonary tuberculosis and they are certainly not due to cachexia or avitaminosis since histologic examination of these hearts shows definite changes due to tuberculosis

Four types of myocardial lesions are found in tuberculosis (1) the large solitary tubercle which may be as large as a fist and may be confused with a cardiac aneurysm (2) inflammatory infiltration of the myocardium which often starts from a tuberculous pericarditis (3) miliary nodules in the course of a generalized miliary tuberculosis (4) interstitial myocarditis (Gallavardin and Cravier) In one series tuberculous myocarditis was found in 10 of 100 cases of pulmonary tuberculosis (Roberts and Lisa)

Rather frequently we find abnormalities in the electrocardiograms of patients with an active exudative tuberculosis when they are examined prior to surgery thiamine deficiency atrophy or other degenerative diseases of the heart must be ruled out in such cases

Perrin et al described heart failure in young subjects caused by tuberculous lesions of the myocardium This etiology however is not proven in their patients

Typhoid Fever and Typhus Influenza Pneumonia Heart muscle involvement in typhoid fever consists largely of degenerative changes but actual inflammatory reactions are the rule in typhus As elsewhere in the body in typhus the inflammation is mainly in and around the vessels In uncomplicated influenza myocardial involvement is unusual but does occur occasionally It is common in pneumonia caused by pneumococci or streptococci

Virus Infections and Rickettsial Diseases The existence of myocardial changes in virus infections has often been demonstrated It appears in the experimental forms different viruses seem to evoke responses peculiar to the agent employed (Pearce) The myocardium may be affected in poliomyelitis In a series of 17 cases of poliomyelitis in which the heart was examined microscopically histologic evidence of myocarditis was found in ten (Saphir) The electrocardiogram was altered in 21 out of 52 patients with poliomyelitis (Frischknecht and Zellweger) and this was considered to be caused by potassium depletion This explanation may be valid for some of these changes Myocarditis appears in mumps Marked changes may appear in psittacosis In the course of an epidemic one of us had the opportunity to observe two physicians ill with psittacosis both had very marked but transient electrocardiographic changes The T waves were deeply inverted in lead I in one case and were inverted in all leads in the other

Electrocardiographic changes during life and perivascular infiltrations in the heart muscle after death have been seen in measles epidemic (viral) hepatitis primary atypical pneumonia infectious mononucleosis (figure 40) rubeola and influenza

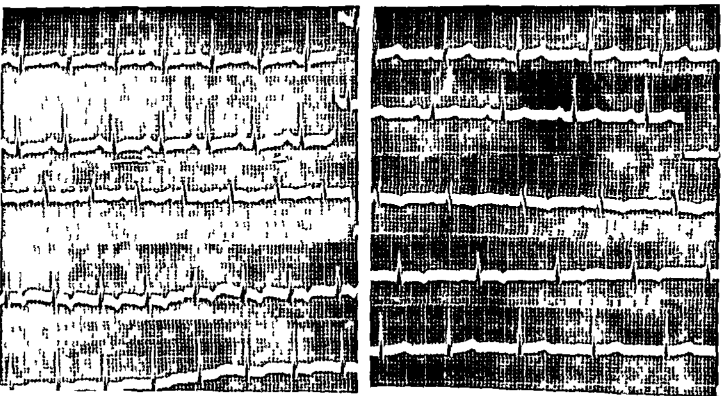


FIG 40 Abnormal T waves in the standard leads as well as in V 2 and V 5 in a 0 year old woman with infectious mononucleosis (a) Twelve days later (b) the electrocardiogram is normal

Cardiovascular lesions occurring in virus diseases have been reviewed by Lyon Rickettsial diseases scrub typhus for example occasionally cause a myocarditis

Acute Nephritis The nature of myocardial involvement in acute nephritis is still problematical but changes in the myocardium are the rule The importance of sudden cardiac failure in acute glomerular nephritis has been known since the classical work of Volhard In a series of 138 cases clinical signs of cardiac damage were found in 71 per cent Opinions are still divided on the question whether this is due to inflammatory reactions in the myocardium to toxic changes or to ischemia resulting from a generalized capillaritis with increased capillary permeability In the interstitial tissue exudate with cellular elements are found The venous pressure is increased in patients with acute nephritis (La Due) and hydrothorax is common (Zdansky)

Drug Allergy Of great interest are the changes occasionally seen after the administration of drugs Electrocardiographic changes followed the injection of arsphenamine (neosalvarsan) Histologic studies have revealed the occurrence of an eosinophilic myocarditis in patients under treatment with this drug Cardiac involvement appeared in one case after the seventh injection, and Charcot Leyden crystals and infiltrations of eosinophiles were found in the myocardium Some of these cases and others reported in the literature also developed a salvarsan dermatitis The mechanism is obviously one of idiosyncrasy or allergy

Every drug allergy and serum sickness may cause changes in the heart muscle resembling myocarditis with a necrotizing arteritis and periarteritis

A similar interstitial myocarditis with a rich infiltration composed of eosinophiles was described following the clinical and experimental use of sulphonamides These findings were denied by others (Fawcett) In all these instances the heart was not exclusively affected but participated in alterations like the other organs

The possibility of allergic changes in the myocardium following the administration of otherwise harmless drugs is established and this may prove a clue to understanding a very peculiar serious affection of the myocardium commonly called Fiedler s myocarditis

Postpartum Myocarditis Occasionally young women suddenly develop dyspnea tachycardia and edema 5 to 30 days postpartum The heart is found enlarged Mural thrombi may cause emboli in the systemic circulation (Sodeman) Severe focal inflammation of the myocardium is noted at post mortem The etiology of this syndrome is unknown and its differentiation from multiple embolisms from pelvic veins is difficult

Dermatomyositis The cardiac changes found in dermatomyositis a collagen disease of obscure origin are also unexplained

Fiedler s Myocarditis This lesion which has been called primary idiopathic acute interstitial isolated and pernicious myocarditis usually affects young adults However it also occurs in children and apparently is not as rare as the few cases reported in the literature would seem to indicate

Grossly the heart may show hypertrophy that may attain considerable proportions The ventricles are involved more than the atria and the left ventricle more often than the right The inner layers of the myocardium usually suffer more than the outer ones The parenchyma itself is only slightly involved In one type there is extreme infiltration with various types of white blood cells sometimes mainly eosinophiles In the second type the lesion is granulomatous with fibroblasts and giant cells but tuberculosis is not responsible

Usually the onset is abrupt and ordinarily the course is one of progressive cardiac failure Fever chills lassitude and anxiety may characterize the onset Two of Saphir's 13 cases died suddenly and some of them had anginal pain Percussion usually reveals cardiac enlargement Ordinarily tachycardia and hypotension prevail The cardiac sounds are often altered and gallop rhythm is frequent The electrocardiographic changes if present are consistent with a diffuse myocardial lesion The disease is fatal within a period of days a few weeks or rarely months Pulmonary and cerebral embolism are frequent

Treatment to date has been futile the fatal outcome seeming to justify the term pernicious myocarditis (Boikan)

The terms essential idiopathic and isolated myocarditis indicate that the heart alone is affected insofar as postmortem studies show The etiology of the disease is unknown Since some other types of myocarditis are definitely allergic the same possibility must be seriously entertained in the pathogenesis of Fiedler's myocarditis It is also uncertain whether the disease is invariably fatal and what if any is its relation to milder forms of myocarditis The relation of Fiedler's myocarditis to the myocardial lesions of avitaminosis will be discussed later in this chapter

The Clinical Picture of Myocarditis

With certain readily understood exceptions dependent upon the etiology and accompanying disease the subjective symptoms and objective signs in all cases of myocarditis are similar Some of them were mentioned in the discussion of tonsillitis (p 250)

Symptoms The subjective symptoms are usually mild and not characteristic *Palpitation is frequent and sometimes annoying General weakness is pronounced* Anorexia and loss of weight are often noted

Precordial pain is a very common symptom appearing without provocation and lasting only a few minutes The pain may be very intense and may radiate to the shoulders and arms

In most cases the above mentioned complaints are not sufficiently striking to draw the attention of an unwary physician to the heart

Signs The paucity of physical signs is explained by the fact that inflammatory foci scattered diffusely in the heart muscle usually do not alter cardiac size or auscultatory phenomena Only the rare more extensive inflammations produce changes detectable by percussion or auscultation

Fever is common in the acute stage but is often first noted by the physician because the patient is unaware of it While the temperature may exceed 38 5° C it may be absent even in a florid myocarditis

Cardiac enlargement is absent or minimal in an otherwise healthy heart but in some instances particularly when the patient does not remain in bed the enlargement may be pronounced Nevertheless this enlargement is usually *transient in contrast to the persistent form encountered in rheumatic valvular* lesions moreover it recedes with striking rapidity

When a decompensated valvular defect with an enlarged heart is successfully treated and compensation is fully restored cardiac size usually remains constant If cardiac size diminishes during treatment it is assumed — correctly in our experience — that a pericardial effusion was present and has now decreased or disappeared However cardiac enlargement may recede considerably in *myocarditis*

Fluoroscopy often reveals very strong pulsations and marked excursions of the cardiac border Cardiac dilatation is often absent when the patient is examined by x ray in the upright position but is detected in the supine position (Zdansky) This is explained by the increased return of blood to the heart resulting in greater filling of the cardiac chambers in the recumbent position

Auscultation often reveals normal pure heart sounds The heart rate is fast and accelerates markedly even on slight exertion but this sign is not always present A systolic apical murmur if present is not characteristic The first or second sound is often split In severe myocardial lesions the heart sounds become distant and impure Gallop rhythm is often present Arrhythmias due to partial A V block are not rare but extrasystoles are rather unusual A progressive anemia occurs in many protracted cases

The electrocardiogram reflects the involvement of the myocardium more often than any other method of examination Alterations are not always evident and are not continuously present even in proven cases They develop only when inflammatory foci exist at definite places in the specific tissue or when large foci are situated in definite areas of the myocardium Since new foci constantly light up and vanish the electrocardiographic changes consisting of widened QRS complexes abnormal T waves and conduction disturbances may be present one day and gone the next Frequent electrocardiograms are necessary and one positive record will establish the diagnosis

Diagnosis If the diagnosis of myocarditis were suspected more frequently it would be more widely appreciated that the affected patients need not manifest symptoms or signs demonstrable by percussion auscultation x ray or even electrocardiography Therefore if patients were examined more often with this diagnosis in mind the lesion would be found in innumerable cases currently unrecognized

Since these patients *must rest in bed and must avoid every unnecessary* demand upon the heart timely recognition is of utmost importance

Probably the connective tissue scars discovered so frequently by pathologists in the heart muscle (fibrosis of the myocardium) in patients dying for diverse reasons but without coronary artery diseases are often due to an old healed myocarditis In view of the frequency of infections and the realization of the incidence of myocardial participation even in mild infections the assertions made in earlier editions of this book should be repeated namely that we believe that only a few individuals entirely escape the occasional presence of small inflammatory foci in the myocardium (myocarditis)

Complications As previously suggested one of the most serious nonpreventable complications is a peripheral embolus originating from a mural thrombus In some young hemiplegics who have no signs of lues or a congenital aneurysm an undiagnosed myocarditis explains the accident

Abscesses form in overwhelming sepsis subacute bacterial endocarditis and myocardial infarction Such an abscess may perforate outwardly Cardiac aneurysms sometimes develop

Prognosis In most cases prognosis is excellent and healing of the lesion is thorough Only in a minority of cases most of them at present still included in the group called Fiedler s myocarditis is the outcome fatal The course of the disease in such cases may be rapid with early death

Treatment Bed rest the eradication of focal infection and antibiotic drugs are the only methods of treatment available If allergy toward a drug is discovered its administration should be discontinued Rest in bed should be enforced as long as electrocardiographic changes fever tachycardia or changes in the character of the heart sounds indicate activity of the myocarditis In infectious myocarditis antibiotics should be given in sufficient doses In the allergic type it is often difficult to find the responsible antigen

MYOCARDIAL DEGENERATION

The diagnosis of myocardial degeneration is justified only if an etiologic factor is detected The myocardium like any other muscle does not degenerate without some extrinsic cause At one time myocardial degeneration was diagnosed in every cardiac patient who did not have a valvular lesion

Cardiac Atrophy

Atrophic changes of the myocardial fibers constitute the most common change in the heart There is rarely a severe wasting disease (tuberculosis a malignant tumor severe anemia or a prolonged debilitating disease) that is not associated with cardiac atrophy These hearts are firm because the connective tissue does not share in the atrophy to a comparable degree the coronary arteries may become tortuous since they also escape atrophy Apart from this simple atrophy brown atrophy is also encountered especially in older individuals These atrophic hearts usually are capable of meeting the demands imposed upon

them by individuals whose activities are necessarily limited although there is a definite decrease in the reserve power

Some of these hearts weigh less than 100 grams Often there is a bradycardia particularly in hunger atrophy The blood pressure falls and the electrocardiogram shows low voltage due to loss of muscular substance

Cloudy Swelling

Among the degenerations in a more strict sense there is the cloudy swelling which accompanies a host of infectious diseases and which may result from intoxications with chloroform as well as many other agents The cardiac involvement is a single example of a widespread process with similar lesions in other parenchymatous organs

Grossly the flabby heart looks like boiled muscle

Diphtheria

An outstanding instance of myocardial degeneration is the involvement of the muscle in diphtheria which too often is called a myocarditis Actually reactive inflammatory processes occur secondarily, like those at the border of a myocardial infarct after coronary occlusion The primary lesion of the heart in diphtheria is a focal degeneration and necrosis of the muscle fibers later a reactive inflammation and proliferation of the fixed tissue cells appear These changes have a toxic origin they are often widespread and the prognosis may be serious Nowhere is the recuperative power of the heart more clearly manifested than in diphtheria If patients survive the acute phase cardiac failure soon disappears a complete atrioventricular block or bundle branch block vanishes and after a few months the patient may present normal cardiac findings This is one of the reasons it was formerly held that the acute cardiac failure was primarily of the peripheral circulatory type that is vasomotor rather than cardiac In rare cases atrioventricular block or bundle branch block persist (Hoel and Perg)

The clinical picture is well known There is hardly a more tragic experience *than that of observing a child pass through diphtheria and suddenly succumb* to a cardiac affection The premonitory symptoms are few in number and often elude detection When present they consist of vague precordial oppression dyspnea and palpitation General weakness is often noted Epigastric pain and vomiting may usher in the acute syndrome and death may occur in a lapse of consciousness Extreme pallor is present Usually there is no fever Often sinus tachycardia partial or complete heart block are observed Extrasystoles are rare The presence of conduction disturbance is considered particularly ominous Even if sudden death does not occur early the final outcome may be dubious for weeks A considerable number of these cases recover and have no permanent sequelae

There is no specific treatment once the myocardial damage develops Bed rest must be strictly enforced for weeks since slight exertion has been known to cause sudden failure Otherwise treatment is symptomatic

Fatty Degeneration in Anemia

This alteration of the heart muscle seems to be provoked by the same causes as those responsible for cloudy swelling the causative factor apparently acts over a long period of time and more intensely This lesion played an important role in medicine up to a few decades ago At present however it is rather uncommon since the modern treatment of anemias has found universal use for it was in this group of conditions that fatty degeneration attained clinical importance This degeneration often involves the entire heart particularly the subendocardial layers causing the picture of the tiger heart Alterations are usually most evident in the right ventricle especially around the papillary muscles Cardiac enlargement and murmurs appear The enlargement is due to dilatation of both ventricles and congestive heart failure (predominantly right heart failure) may follow With cardiac dilatation and the acceleration of blood flow consequent to the anemia systolic and occasionally diastolic murmurs become audible and very often lead to the erroneous diagnosis of a rheumatic valvular lesion The cardiac output becomes elevated when the hemoglobin level falls to 7 Gm per 100 ml of blood There is a reduced blood volume in anemia and peripheral arteriolar dilatation The circulation time is abnormally short

While relative mitral (and even relative aortic) regurgitation occurs the systolic and diastolic murmurs in these patients usually arise from the veins near the heart and are the result of the increased speed of blood flow

Fat Infiltration

This is a rare lesion in obese individuals Not only is the subepicardial fat increased but true infiltration occurs in the myocardium This condition is also more common in the right ventricle Owing to the fact that small interstitial cells when they become fat cells have an increased size the myocardial fibers are pushed apart an event which is important when the thin wall of the right ventricle is extensively permeated by fat cells When fat infiltration is moderate it seems to lack functional significance When extreme (a rather rare occurrence) it may produce right heart failure and even death by rupture of the right ventricle (Smith and Willius)

Thiamine Deficiency (Beriberi)

Cardiovascular involvement as the result of nutritional disturbances have been studied for many years The type following thiamine deficiency was observed first in East Asia and in the East Indies

Incidence Cases of beriberi due to nutritional disturbances are observed in the Western Hemisphere relatively often They are found in alcoholics drug

addicts pregnant women and individuals who voluntarily (faddists) or on medical advice follow special diets These individuals frequently develop severe cardiac changes from avitaminosis Many patients of this kind may be seen in a hospital ward each year Even on a normal diet cardiac damage may result from an abnormal absorption or an abnormal utilization of thiamine

Mechanism Lack of thiamine disturbs tissue oxidation The amount of tissue cocarboxylase is diminished Pyruvic acid and lactic acid are not broken down and are found in the blood in larger quantities In thiamine deficiency *Raab found an excessive accumulation of adrenosympathetic substances in the* heart muscle which may explain the short P P interval in the electrocardiogram

Symptoms and Signs Besides general weakness the usual symptoms of heart failure — dyspnea on exertion swelling of the ankles and palpitation — are present

Examination reveals a collapsible pulse which may resemble the Corrigan pulse of aortic insufficiency The diastolic blood pressure is low a systolic sound is heard over the peripheral arteries and a capillary pulse is present These phenomena are at least in part due to a general peripheral vasodilatation The signs are more pronounced in the oriental type of beriberi but are not completely absent in the occidental form (Aalsmeer)

Usually the heart rate is increased The heart is diffusely enlarged particularly to the right the pulmonic arc is prominent Evidence of right (and left) heart failure occurs Palpation reveals marked hypermotility of the cardiac area This may be connected with the greater amounts of adrenalin and related compounds which have been found in the heart muscle of rats in vitamin B_1 deficiency (Raab and Suplee)

The heart sounds are often impure Gallop rhythm may appear but arrhythmias are rare The blood pressure is often low and the velocity of blood flow is increased

The patient may show other evidence of vitamin deficiency In tropical beriberi electrocardiographic alterations are infrequent Apart from a relatively short P I interval little has been found even when marked cardiac dilatation and congestion prevailed Definite depression of the RS T segment and T wave changes were described in occidental beriberi and in our experience they are common (figure 41) Occasionally the P R interval is prolonged and the QRS complexes are widened The discrepancy between the electrocardiographic findings in oriental and occidental beriberi does not seem to have been explained In all probability the lack of other vitamins plays a role While in oriental beriberi right ventricular failure with right outflow tract dilatation is common it is rare in the occidental type

Pathology Hydropic degeneration of the myocardium originally seemed to explain the severe myocardial lesion The water content of the heart muscle however is not increased in experimental beriberi In recent years focal myocardial necrosis has been found in avian and mammalian hearts during thiamine deficiency The necrosis is often visible to the naked eye Just as in other local

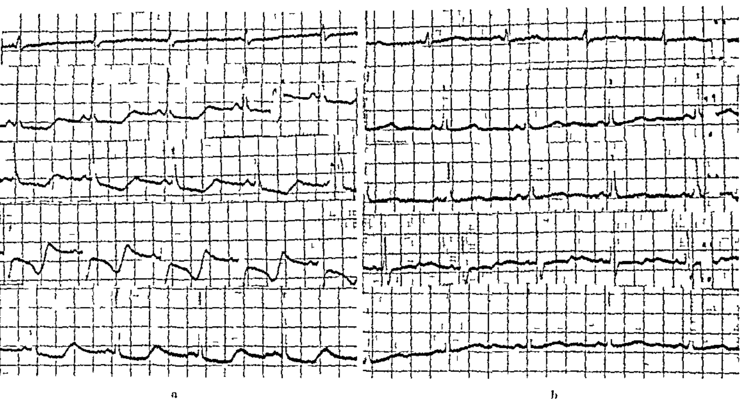


FIG. 41. An electrocardiogram in the standard leads as well as in V2 and V5 of a 49 year old woman suffering from alcoholism. The P-R intervals measure 0.11 second and the RS-T segments and the T waves are abnormal (a). After a week during which thiamine chloride was given, the electrocardiogram (b) was almost normal.

degenerations the necrotic area may be secondarily infiltrated with leukocytes scars form during healing Sometimes the endocardium becomes thick and the *resulting mural thrombi may cause embolism The histologic changes may* closely resemble those seen in Fiedler s myocarditis For these reasons the question has even been raised whether individuals supposedly suffering from idiopathic or essential myocarditis did not in reality have a thiamine deficiency (Dock)

It is possible that further investigation will show that allergic and nutritional disturbances explain many of the hitherto puzzling cases of essential myo cardial lesions It is evident furthermore that nutritional disturbances in cardiac patients may damage the heart and aggravate existing conditions Inadequate nutrition is common in patients with chronic cardiac disease

Therapy The degree of myocardial necrosis and reactive inflammation may explain why the administration of large doses of thiamine chloride (100 to 150 mg daily) to some patients with a beriberi heart leads to rapid recovery while in others prolonged treatment is necessary Clearly hearts in which anatomic changes have already appeared require a longer time for recovery If the heart *muscle has been irretrievably damaged improvement becomes impossible*

When there are disturbances of absorption large doses of thiamine chloride must be given parenterally for a longer time than in cases of thiamine deficiency due to lack of intake The absence of cheliosis of abnormal reflexes and of tongue changes does not speak against the diagnosis A deficiency of other components of the vitamin B complex need not be present

Other Types of Degeneration

Myocardial Lesions Caused by Disturbances of the Electrolyte Balance We are only *now beginning to understand the disturbances of the myocardium* caused by abnormal electrolyte content of the blood and heart muscle The disturbances of potassium content are known best since they cause electro cardiographic as well as histologic changes in the heart muscle

In patients with a great variety of lesions hypopotassemia or hypokalemia can develop It is seen in chronic diarrhea particularly in infants in diabetic acidosis in sprue after surgical operations following the administration of desoxycorticosterone or cortisone and in aldosteronism The changes may be particularly striking after the intravenous injection of glucose indeed such therapy may be dangerous in patients with the above mentioned conditions

The patient may experience dyspnea Cardiac enlargement is found Irregular rhythms interference between sinus and A V rhythms and extrasystoles appear

Histologically in animal experiments (pig rat) and in man (McAllen) pin point necrosis of myocardial fibers with infiltration by polymorphonuclears and bands *of fibrotic tissue are seen* Similar lesions *(interstitial myocarditis)* (Keye) have been reported in Friedreich s ataxia scleroderma and progressive muscular dystrophy It is of interest that in rats the myocardial necroses which appear on a potassium low diet are prevented by thiamine deficiency (Follis)

The electrocardiographic changes consist of a depression of the PS T segment and very prominent U waves (Bellet). An accompanying prolongation of the Q T interval is caused by a hypocalcemia present at the same time. It is not yet decided whether the electrocardiographic changes are more related to the serum

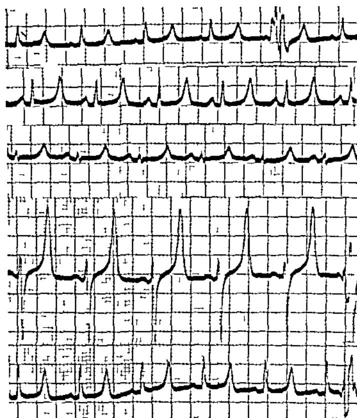


FIG. 49. The electrocardiogram of a 34 year old woman with acute renal failure and hyperpotassemia (6 mEq.). The T waves in the standard leads as well as in V 2 and V 5 are abnormally high and tent like. They have a small base and the ascent and descent are *almost symmetrical.*

than to the myocardial potassium level. In congestive cardiac failure and in a variety of myocardial diseases the K content of the myocardium is diminished. Large doses of digitalis have the same effect. In some patients with large myocardial infarctions the potassium level in the blood rises.

Hyperkalemia as seen in azotemia, Addison's disease or in untreated diabetic acidosis, great muscular weakness, and mental confusion may appear. The electrocardiogram shows typically huge T waves with small bases, peaked, reaching sometimes the height of the R waves. With rising levels of potassium intraventricular block, arrhythmias, and atrial paralysis appear.

Figure 42 shows the electrocardiogram in a moderate figure 43 in an advanced hyperkalemia Figure 44 shows patterns of hypo and hyperkalemia in the same patient

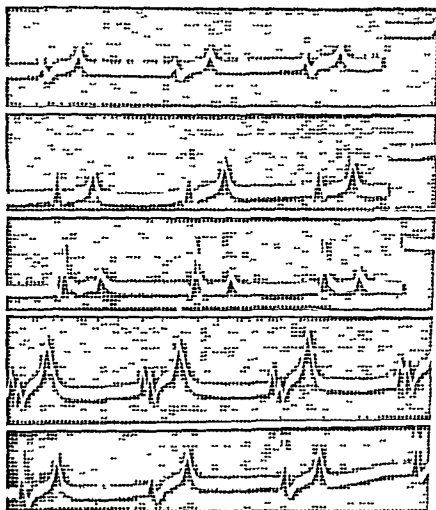


FIG 43 Pattern of hyperpotassemia in a patient with chronic nephritis and renal failure The T waves show a similar pattern to that in figure 42 the QRS complexes are slurred and widened and the sinus rhythm is replaced by an atrioventricular rhythm

Other Types Several degenerative processes in the heart muscle e g those caused by hypothyroidism or toxic doses of digitalis will be discussed under appropriate headings but a few others may be noted at this time Simple hyaline degeneration may occur in the interstitial tissue and in the blood vessels Zenker s hyaline degeneration with swelling and rupture of the fibers occurs in typhoid fever when massive this form of coagulation necrosis may cause circulatory disturbances

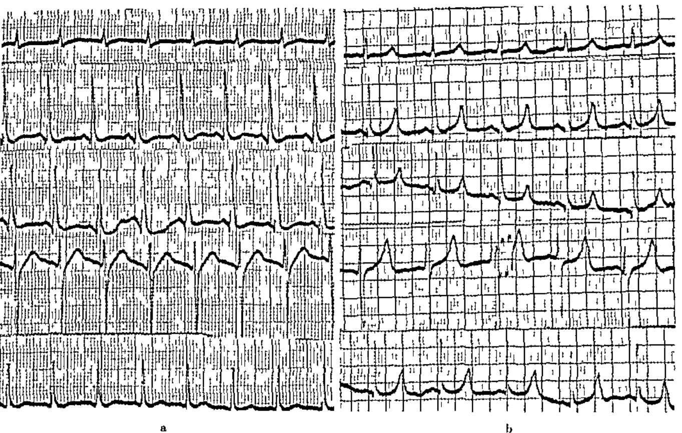


Fig 44 A 26 year old woman had a cholecystectomy with prolonged drainage The electrocardiogram shows the pattern of hypokalemia with depressed RS-T segments and absent T waves (a) Hyperkalemia developed (b) after too energetic therapy

As a mesoblastic structure the heart may also suffer from primary as well as secondary amyloidosis In primary systemic amyloidosis the heart is involved in 80 per cent of the cases The clinical picture may simulate pericardial adhesions As in other degenerative cardiac diseases only T wave changes are visible in the electrocardiogram Primary cardiac amyloidosis occurs most often in the elderly patients The diagnosis is usually missed since coronary sclerosis is suspected

Myocardial damage due to trauma or caused by physical agents (x ray) will be discussed in a later chapter

Degenerations of Unknown Etiology During the last war Bedford and Konstam described a severe myocardial disease in West Africans that affects young people and is of unknown etiology Signs of heart failure with dyspnea and edema suddenly appear general weakness is pronounced and the blood pressure is low Subendocardial necrosis is found and strands of fibrotic tissue are present in the myocardium Mural thrombi are common Rarely there is an eosinophile reaction A deficient diet was considered as etiologic and prolonged malnutrition was actually found to induce similar changes (Toreson) Subsequently it was noted that the histologic changes are different from those seen in beriberi Furthermore, the illness certainly occurs without malnutrition Cray found the syndrome in two Europeans who had visited West Africa The possibility of a virus infection has been discussed

The disease has also been observed in the United States (McKusick and Cochran)

Clinically these patients are admitted with evidence of congestive heart failure Relative mitral and tricuspid insufficiency caused by involvement of the papillary muscles and thickening of the valves leads to the wrong diagnosis of a rheumatic valvular lesion Men are affected more often than women The clinical picture may simulate that resulting from pericardial adhesions with constriction of the heart (Loeffler) The situation rapidly deteriorate and there is no response to therapy

This syndrome is probably related to the syndrome described by Loeffler in which there is endocardial fibrosis with thrombosis and eosinophilia It may also be noted that after experimental stress Selye found similar strands of fibrotic tissue in the myocardium as a sign of his general adaptation syndrome

Also of unknown mechanism are the myocardial changes frequently seen in Friedreich s ataxia progressive muscular atrophy and myotonia atrophica In the latter condition an abnormal electrocardiogram was found in 68 3 per cent of the cases Bundle branch block and atrioventricular block are common

Paget s Disease Involvement of the circulation is common in Paget s disease Paget himself described the increased blood supply to the involved bone with increased warmth over the involved area With widespread involvement of the bones the cardiac output was reported as amounting to 13 3 liters per minute in one case (Edholm et al) In addition such patients often have hypertension and an increased *incidence of atherosclerosis* Kyphoscoliosis is common and may

contribute to the circulatory embarrassment Lequime and Denolin found at rest no increase of circulation it appeared however following exercise provided abnormality of the bone was widespread

CORONARY SCLEROSIS

Introduction

Atheroma is a lesion caused by lipid deposits in the intima In atherosclerosis in addition to such deposition there is a proliferation of the intima and calcium deposits may appear Arteriosclerosis is in itself not an entity three main types of arteriosclerotic processes being distinguished at present

(1) *Monckeberg s Sclerosis* Medial calcification of the arteries Monckeberg s sclerosis is a *more or less physiologic phenomenon Small deposits of lime salts* appear very early in the media of human arteries particularly in the pelvic vessel They are a regular finding in patients beyond the age of twenty (Clawson) and are more common in males than in females When this process is somewhat more pronounced it is referred to as Monckeberg s sclerosis It occurs most often in the femoral pelvic radial and temporal arteries it is rare in the coronary arteries The lack of cholesterol deposits in the intima distinguishes this process from true arteriosclerosis but the two lesions may be combined Since medial sclerosis does not narrow the arterial lumen it ordinarily has no clinical significance The small calcified areas may be present as nodules or more commonly as rings and give rise to so called corduroy arteries If these rings fuse in continuous calcification pipestem arteries will be felt when the peripheral arteries are palpated

Physicians should be aware of the great incidence of this process since patients sometimes become very apprehensive when lime salt deposits are found in the arteries of the abdomen the pelvis or the extremities on the occasion of an x ray examination performed for some other reason

A similar process can be produced in animals by injections of epinephrine by overdosage with vitamin D and by prolonged radiation with ultra violet light Examples of medial calcification in the newborn have been described

(2) *Arteriolosclerosis* A second type of arteriosclerosis is more accurately described as *arteriolosclerosis The term is applied to the arteriolar involvement* that occurs in hypertension It does not seem to depend upon the age of the patient Its relation to the third type is not clear Arteriolosclerosis will be discussed in association with hypertension

(3) *Atherosclerosis* Atherosclerosis is the chief cause of coronary artery pathology The following pages are devoted to this type of arteriosclerotic process

Atherosclerosis — Pathology

The lesion is seen in early youth The milk streaks in the aorta are due to the presence of foam cells in the intima They are found in most children over 8 years of age The mitral valve is affected particularly often at times even in

infancy (Aschoff Hirsch) The high cholesterol content of the food at this age may be responsible Lipid substances deposited in the intima of arteries and valves in early childhood are readily absorbed but the capacity for reabsorption disappears in later years The atheromatous plaques become larger and reabsorption does not take place

In children the atheromatous plaques are situated within the intima The plaques contain — as does the blood — cholesterol cholesterol esters phospholipids and dihydrocholesterol Later on beginning with the third decade they are more prominent and narrow the lumen of the artery since intimal proliferation becomes more pronounced

The left coronary artery is involved earlier and more often than the right (108 times out of 120 cases) The process is more common near the origin of the coronary artery Lime salts are deposited later Thin walled capillaries grow into the atherosclerotic area from the adventitia and the lumen of the artery when the subject reaches the fourth decade (Wolkoff) The importance of these vessels for the development of coronary thrombosis will be discussed in a later chapter

White plaques of lipid deposits appear in the aorta and valves in infants they are present in the main coronary arteries in patients 18 to 20 years old In subjects over 30 the chief branches are involved and between 50 and 60 fibrous prominent plaques which may obstruct the lumen are found also in the smaller tertiary branches of the coronary tree (Wolkoff)

Thickening of the intima is a physiologic process characteristic for the coronary arteries (Dock) In patients between 40 and 50 years of age the thickness of the intima of otherwise normal coronary arteries may surpass the thickness of the media (Wolkoff) This is less pronounced in women

Etiology

Lipid Metabolism Since the classical experiments of Anitschkow which demonstrated the increased incidence of atheromatosis in rabbits fed large amounts of cholesterol new data have been obtained regarding the relation of lipid metabolism to atherosclerosis Nevertheless the problem is far from solved

Little is known about cholesterol metabolism It is certain that cholesterol can be formed in the body by building stones as simple as acetate derived from carbohydrates fats or proteins But the transport the regulation of cholesterol levels and details of its function in the body are unknown According to Certler et al the values of the different lipids in the blood are higher in mesomorphic individuals Lower levels of serum lipids were found in normal individuals aged 80 to 100 years old if compared to middle aged persons (Goldbloom and Faber)

With regard to the absolute level of cholesterol and cholesterol esters it is certain that normal levels may be found in patients with severe atherosclerosis while high abnormal levels are seen without it However the following laboratory findings are obtained in most patients with atherosclerosis

THE CHOLESTEROL PHOSPHOLIPID RATIO In addition to cholesterol the phospholipids of the blood represented for the most part by lecithin are of

importance They act as stabilizers of the cholesterol protein molecules Even a marked elevation of the serum cholesterol often does not lead to atherosclerosis when the cholesterol phospholipid ratio is normal that is when the phospholipids are also present in larger amounts and in their normal relation to cholesterol Thus in familial hypercholesterolemia the *phospholipids are not increased* the cholesterol phospholipid ratio is high and atherosclerosis is common on the other hand the latter disease is rare in idiopathic hyperlipemia because here the phospholipids are also increased

THE BETA LIPOPROTEINS The cholesterol molecules are not free in the serum but like the phospholipids they are combined with *giant protein molecules* These molecules called lipoproteins consist of alpha lipoproteins the protein molecules being derived from alpha globulins and the beta lipoproteins derived from beta globulin The total cholesterol in the alpha lipoproteins is diminished but it is increased (70 per cent) in the beta lipoproteins in patients with atherosclerosis

PHYSICAL CHARACTERISTICS OF THE LIPIDS With the ultracentrifuge Gofman and his co workers found lipoproteins of different sizes and densities These large molecules float at different levels with a certain speed of the ultracentrifuge and are *classified according to Sf (Svedberg flotation) units* Molecules which *flotate within a range of Sf 10 to 20 and Sf 20 to 100 units were found to be important* in relation to atherosclerosis Feeding a cholesterol and fat rich diet increases the amount of these molecules a diet free of fat and cholesterol diminishes their amount in the blood Among patients with myocardial infarction 91 per cent are said to possess a larger number of these molecules in the serum there is a particularly *strong association between atherosclerosis and levels of Sf 10 to 20*

The relation between atheromatosis of the coronary arteries and the Sf levels is said to be better than that of the cholesterol values While some confirmation of this statement is available additional data must be collected before further conclusions are drawn It must be emphasized that in the individual case all the values mentioned above may be normal and advanced coronary sclerosis can exist however when groups are studied the abnormal values are prevalent

HYPERCHOLESTEROLEMIA AND *CORONARY SCLEROSIS* *Diseases associated* with large amonts of lipid (cholesterol) in the blood have a proclivity for the development of atherosclerosis and coronary sclerosis in particular as a complication Thus these processes complicate hypothyroidism rather regularly

In diabetes the disturbance of carbohydrate metabolism is usually associated with altered fat metabolism and coronary as well as general atherosclerosis appear more often than in the general population moreover these lesions appear at an earlier age Since the introduction of insulin diabetic coma has become rare and atherosclerotic cardiovascular disease has become the most common cause of death in diabetics It has been estimated that more than 90 per cent of diabetics whose disease has lasted more than ten years have generalized *atherosclerosis*

a low calorie fat poor high carbohydrate diet has been recommended to prevent this arterial lesion While the evidence at hand is not sufficient to prove that diabetes can initiate atherosclerosis there is no doubt that in diabetes the vascular atherosclerotic changes are augmented and accelerated While some believe that careful control of the diabetes can prevent atherosclerosis (Joslin Dunlop) others deny this

Atherosclerosis has been described in nephrosis (Weiss and Minot) The disorder is also common and hereditary in some types of xanthomatosis (e g Hand Christian Schuller disease) which are associated with a high blood cholesterol In certain types of obesity or cholelithiasis coronary sclerosis is common Statistical investigations indicate that diets containing excessive amounts of fat favor the appearance of atherosclerosis

Atheromatosis of the aorta the result of cholesterol feeding is accelerated in experimental animals by castration thyroidectomy and the administration of posterior pituitary extracts Administration of iodine compounds prevents the appearance of atherosclerosis induced by feeding cholesterol in rabbits

The investigations of Bronte Stewart et al are important because they confirm the finding that in general the higher the economic level of their patients the higher the serum cholesterol There was a close correlation between intake of fats and the cholesterol level The protein intake did not influence the results Olive oil and different fats with a high content of unsaturated fatty acids depress the serum cholesterol level So does cottonseed corn oil and soy bean oil (Kinsell et al)

Unsaturated fatty acids are those which have double bonds in the carbon chain The degree of unsaturation is measured by their iodine number The essential fatty acids (oleic acid linoleic acid and arachidonic acid) prevent lipemia after ingestion of fats and eggs and depress the beta phospholipids in the blood

Pyridoxin Deficiency of vitamin B_6 causes in monkeys a lesion similar to human atherosclerosis (Rinehart and Greenberg) Pyridoxin is involved in the formation of unsaturated fatty acids (Schroeder) The intake of 6 mg of pyridoxin daily has been recommended for prophylactic reasons

Lesions of the Intima According to some the deposition of lipoids (cholesterol esters) is the primary factors whereas others believe that some lesion of the arterial intima represents the primary alteration Abnormal metabolism of the tissues and abnormal enzyme function have also been considered

Inflammation The part played by inflammation is illustrated best by syphilitic aortitis where secondary atheromatosis is common The appearance of atherosclerosis as a consequence of other kinds of arteritis is often discussed but remains unproven Duguid believes that nonoccluding thrombus formation in the arterial intima leads to a picture resembling atherosclerosis

Mechanical Factors These seem to play an important role The atherosclerotic changes in the heart valves appear at places exposed to the greatest

mechanical strain these are the aortic surface of the aortic valves and the ventricular surface of the mitral valves Atherosclerotic processes are also more frequent at the bifurcation of arteries Even trauma seems to play some part in the development of local atherosclerosis

Hypertension likewise seems to be a factor Coronary sclerosis was found in 20 per cent of the hypertensive subjects in a series of 4678 autopsies while it was present in only 0 2 per cent of those with normal blood pressure Hypertension seems to be an accentuating and accelerating factor rather than a causal one in atherosclerosis

Atherosclerosis is common in the lesser circuit in conditions in which the pressure is high e g cor pulmonale and congenital heart disease

Adiposity An increased incidence of atherosclerosis in the obese is often stressed but occasionally is denied The denials are particularly concerned with a lack of greater incidence in women

Tobacco The relation of smoking to the occurrence of coronary sclerosis is not fully elucidated Many assume the incidence of coronary sclerosis is increased in heavy smokers Some believe that an increased output of epinephrine under the influence of nicotine is responsible for the coronary sclerosis of smokers Statistics showing that tobacco shortens the duration of life were found to be more significant as the amount of consumed tobacco increases (Pearl)

It is certain that nicotine may induce functional narrowing of peripheral vessels but whether this will cause atherosclerosis is still undecided

Other Factors It is interesting that ultraviolet irradiation of cholesterol and egg yolk inhibits their atherogenic property experimentally (Altschul) Alloxan diabetes in rabbits does not lead to atherosclerosis and even prevents this lesion following cholesterol feeding However the phospholipids are markedly increased in these conditions

Sex

There is a distinct difference in the incidence of coronary sclerosis in the two sexes — the disorder is much less common in younger women unless they suffer from hypertension or diabetes

In patients under 40 years of age the disease is much more common in men After 60 years the incidence is the same in both sexes This relation has often been attributed to the influence of the sex hormones Recent experiments showing the prevention of atherosclerosis by estrogen therapy serve as a confirmation The degree of atherosclerosis in women with bilateral oophorectomy is greater than in women in general (Wuest et al) Estrogen seems to clear the plasma of high molecular lipids Estrogens correct pathologic protein lipid relationship Hypogonadism in both sexes is associated with an increase of alpha lipoproteins they are increased by stilbestrol and reduced by methyl testosterone

Coronary sclerosis begins earlier in males The peak of incidence is reached between 55 and 59 In women the rise is slow from the ages of 40 to 70 years (Peel)

Even in men the oral administration of estrogens tends to correct pathologic protein lipid relationships of the survivors of myocardial infarction Methyl testosterone has an opposite effect (Russ Eder and Barr) The mechanism of this action is unknown

Race Eating Habits

A racial factor has been postulated for there is some evidence to suggest that coronary sclerosis is particularly common in Jews and relatively infrequent in Negroes It seems however that it is not the race but the dietary habits that are responsible There is no doubt that Negroes in Africa and Chinese in China have less atherosclerosis but show the same incidence as soon as they adopt American eating habits In areas of the world where little fat is consumed investigations show a lesser incidence of hypercholesterolemia and of atherosclerosis

Dramatic proof of this situation was provided during the war In Finland Norway and Sweden the incidence of deaths due to atherosclerosis fell during the war when the consumption of fat was diminished and rose again with the resumption of customary eating habits In Denmark where fat consumption rose during the Second World War the opposite trend of mortality due to heart disease as the result of atheromatosis occurred (Malmros Strom and Jensen)

Kuczynski s investigations on the nomads of the Kirgiz steppe where the mortality among young males from coronary disease was tremendous are well known The food consisted chiefly of large quantities of mare s milk and its products

One has to consider that with diminished consumption of fat the intake of proteins also is often diminished The diet too is frequently undercaloric

Age Heredity

Coronary sclerosis is definitely not a disease of any particular age for it occurs in young people and it may be absent in the aged Occasionally marked coronary sclerosis and even coronary thrombosis is seen in infants it has also been found in siblings (Menten and Fetterman)

It is astonishing how frequently patients with coronary sclerosis reveal that the same lesion is present in other members of the family We have observed one family in which one brother died of coronary sclerosis at 46 another developed left ventricular failure gallop rhythm and marked changes in the electrocardiogram due to coronary sclerosis at 45 a third brother had a coronary thrombosis at 50 and a fourth brother was discovered to have hypertension when he was 42 Heart block due to coronary sclerosis has been observed to develop in twins at approximately the same time and an involvement of the same artery must be assumed Abnormal cholesterol metabolism is also hereditary

It is important to note that coronary sclerosis may be found without evidence of athero clerosis of the aorta or in the peripheral arteries

Incidence

Anatomic investigations on otherwise healthy soldiers in wartime have shown that at the ages of 18 to 20 coronary sclerosis is found in 40 per cent of the necropsies The average age of American soldiers killed in action in Korea was 22 2 years and the incidence of sclerosis was 77 3 per cent (Enos et al) In necropsies on 65 young soldiers during World War I atherosclerosis of the aorta and coronary arteries was 44 6 per cent of all cases In another series of 75 additional cases the same observer found atherosclerotic changes in 57 3 per cent (Monckeberg) The descending branch of the left coronary artery was most often affected

In 1000 consecutive autopsies Allan found coronary lesions in 371 the youngest patient affected was 13 years old In over 50 per cent of these cases a myocardial fibrosis had resulted from the coronary lesion From another study (Clawson) of 928 cases of coronary sclerosis it was concluded that this affection accounts for 25 per cent of all deaths from heart disease (exclusive of congenital heart lesions) and of 4 per cent of all deaths in individuals over 6 months old While myocarditis and diphtheritic involvement are the most common affections of the heart muscle in youthful patients coronary sclerosis with its resultant myocardial fibrosis is by far the most frequent affection in older individuals

According to Pyle and Russell the mortality from coronary sclerosis is highest among physicians and lowest among gardeners agricultural laborers and workers in chemical processes Others found no greater incidence among physicians than in the general population but a higher rate has been claimed among men engaged in sedentary occupations Morris found a lower incidence of coronary sclerosis in physically active people However in miners aged 55 to 64 the incidence of coronary sclerosis was 38 per cent (Thomas et al)

At the age of 35 and over a twofold to threefold increase has occurred in England and Wales in the death rates attributed to coronary disease in the last 15 years (Martin)

Further details will be discussed in the chapter on angina pectoris

Symptoms

Sometimes the lesion is betrayed by the symptoms of angina pectoris This occurs when the atherosclerotic process has led to the stenosis of a coronary artery the occlusion of the involved artery leads to the syndrome of myocardial infarction Very often however pain is absent even when a large branch of a coronary artery is completely blocked While reliable statistics are not available pain is mentioned in the history of only a minority of cases with fully developed coronary sclerosis

In many patients the lesion is asymptomatic Some consult the physician for vague complaints like fatigue or loss of appetite Some have gastrointestinal symptoms such as persistent meteorism eructations alternating diarrhea and constipation Since these symptoms are often pronounced in patients ...

circulation is fully compensated co existing sclerosis of the mesenteric vessels may be suspected if the action of reflexes and colonic spasm can be excluded

In many patients who consult their physicians for complaints relating to *hypertension or diabetes* evidence of coronary disease is discovered accidentally

In most cases the lesion remains unrecognized and unknown to the patient until some complication like coronary thrombosis or heart failure appears

Signs

Very few signs may be called pathognomonic for coronary sclerosis the most reliable is the discovery of a sclerotic coronary artery in an x ray film This finding however offers little diagnostic help because medial sclerosis without obstructive atherosclerosis may show deposits of lime salts

From a factual standpoint the diagnosis of coronary sclerosis one of the most prevalent cardiac lesions is made only by inference If a patient complains of anginal pain we may infer the existence of a coronary sclerosis on the basis of known facts If a patient over 40 years of age has evidence of heart failure or of cardiac dilatation with changes in the electrocardiogram indicative of myocardial involvement and there is no other cause (myocarditis uncomplicated hyper tension avitaminosis or infection) one may assume that coronary sclerosis exists This assumption is supported by the discovery of atherosclerosis in other arteries such as those of the fundus retinae

The diagnostic difficulties are exemplified by a study of 86 cases which came to necropsy with such diseases as carcinoma gastric ulcer and cirrhosis of the *liver and which showed marked coronary sclerosis (Willius and Brown) The* ages of the group varied from 33 to 81 years Seventy eight per cent were males Only 24 per cent had anginal pain In 40 per cent of the patients there was no subjective or objective evidence of cardiac disease

Accordingly at necropsy one is often surprised by the severity of the alter ations in the coronary arteries and even by those in the myocardium when the asymptomatic patient has presented no evidence of cardiac disease on clinical examination Physicians who appraise the hearts of elderly individuals prior to operation accept a great responsibility and should always bear in mind our limitations of knowledge It is better to state that the examination does not disclose coronary sclerosis than to say that coronary sclerosis is absent

Often the first sign of atherosclerosis is a harsh systolic murmur over the apical area or over the aorta At first this murmur may be audible only after exertion but later it is permanent In all probability this murmur depends upon sclerotic changes in the aortic valve so that it is not a direct sign of coronary sclerosis Nevertheless it is significant as indicative of an atherosclerotic process and is important when found in relatively young individuals In 86 consecutive necropsies in which coronary sclerosis was found 51 per cent (44 cases) had sclerosis of the mitral or aortic valves In 17 per cent both valves were involved The remaining physical findings are similar to those elicited in other myocardial lesions and will be discussed in a later section

The electrocardiogram has been a great diagnostic aid and accounts for most correct diagnoses Nevertheless a normal electrocardiogram does not preclude the presence of advanced coronary sclerosis The electrocardiogram may remain normal when the lumen of the vessel is not markedly narrowed and therefore no myocardial ischemia develops The same thing happens when the lesions are small or when they are located in areas not clearly represented in the electrocardiogram One should also remember that profound changes in the electrocardiogram may vanish rapidly with the development of scar tissue and the progress of healing

At present coronary sclerosis is diagnosed much more frequently than in former years Whether or not this is due to an actual increased incidence is not fully decided While pathologists report an increase it is equally true that they inspect the coronary arteries more carefully than in the past The refinement of methods of examination and the fact that the term coronary sclerosis is generally used when formerly a diagnosis of dropsy cardiac insufficiency angina pectoris and the like would have been made are certainly responsible for the apparent increased incidence of the lesion

Therapy

There is no specific therapy for coronary sclerosis

All types of fat should be restricted Plant sterols are not absorbed from the human gastrointestinal tract in appreciable amounts However they must be restricted as well since cholesterol values in the serum rise when vegetable fat is added to the diet of patients on cholesterol poor food

The ingestion of neutral fat should also be restricted since fat facilitates the absorption of cholesterol A reduction in the caloric intake in general seems to be important (see later) The rice diet and similar fat free diets have shown that it is possible to diminish the cholesterol content of the serum by 20 to 40 per cent

The so called lipotropic substances such as inositol choline and methionine seem to be without value Serum cholesterol levels are said to be lowered by polysorbate 80 choline inositol complexes This agent increases the stability of lipid emulsions

Estrogens seem to clear the plasma from high molecular lipids (Pick et al) They increase the phospholipids in cockerels lower the cholesterol phospholipids ratio and atherosclerotic plaques are perhaps reabsorbed We recommend continuous administration of estrogens to all postmenopausal women with hypertension diabetes or a family history of coronary artery disease In man unfortunately this therapy leads to unpleasant side effects

Estrogens have to be given in large amounts in order to be effective in changing the abnormal lipid pattern of the blood to a normal one This problem is under study at the present time

Soybean sterols mainly sitosterol admixed to the diet has been said to lower plasma cholesterol markedly It may interfere with the absorption of cholesterol

(Peterson) Eight grams of sitosterol are given before meals (Best et al) However Wilkinson et al working with ambulatory patients were unable to achieve sustained reductions in the level of the blood cholesterol The substance needs further evaluation

Cytellin a mixture of beta sitosterols with dihydrobeta sitosterols is available One gives 8 to 10 grams 2 to 3 tablespoons per day orally in the form of a suspension

Patients with hypercholesteremia may develop thromboembolic phenomena when they are under therapy with corticotropin or cortisone (Adlersberg et al) In patients with hypercholesterolemia large doses of nicotinic acid cause the blood lipid pattern to change toward normal (Altschul et al) Three to 6 grams of nicotinic acid are given daily Side reactions such as flushing and pruritus diminish rapidly after a few days of treatment Urticaria and vomiting disappear within a few days after discontinuation of the treatment and do not reappear when treatment is resumed

Essential unsaturated fatty acids particularly linoleic acid are now recommended in capsule form in order to lower the cholesterol level of the blood Nicotinic acid and pyridoxin are added

In addition to diet hormonal hereditary and other factors play a role but a fat poor diet is the strongest weapon available at present against atherosclerosis

The chylomicrons which appear in the blood following the absorption of fat disappear following the intravenous injection of heparin (Hahn) but the use of heparin injections (daily or twice weekly) as recommended did not yield convincing results in patients with evidence of coronary sclerosis It has been claimed that this therapy improves angina on effort and similar complaints rapidly Whether it prevents the progression or development of atherosclerosis is not established

MYOPATHIES

There is a small group of cases in which clinical and pathologic examination including histologic sections fail to reveal the diagnosis and the nature of the myocardial lesion The heart is enlarged and evidence of heart failure is observed prior to death but the coronary arteries are normal and patent No previous hypertension existed histologically the myocardium seems normal The expression myopathy has been coined for these cases Clinicians occasionally use the term myocardosis Wuhrmann defines myocardosis as a change in the myocardium without cellular interstitial infiltrations there is evidence of fatty degeneration and cloudy swelling These cellular degenerations are encountered in Laennec s cirrhosis in hepatitis in the nephrotic syndrome in alcoholism and sepsis and are explained by a dysproteinemia If the cells die myocardial fibrosis may follow

Undoubtedly many patients placed in this category belong to the group of nutritional disturbances (e g thiamine deficiency) While microscopic changes

are demonstrable in advanced stages of the lesion in all probability there are periods in which the rather crude histologic methods now available fail to reveal an alteration of the myocardial fibers

It is precisely in myocardial disease that the unreliability of anatomic and histologic methods of examination impresses one most distinctly A normal microscopic appearance does not show whether the heart functioned normally and efficiently It has been pointed out that it is often impossible to explain heart weakness and cardiac death anatomically Often the pathologist cannot tell why a patient who responded excellently to digitalis for years suddenly ceased to react to treatment When asked whether the heart muscle was sufficiently strong to compensate for a valvular lesion the pathologist can answer only by examining the liver lungs or kidneys the heart itself reveals nothing

This experience was responsible for the chemical study of the heart muscle with the hope of finding significant changes which were not disclosed by histologic methods Changes were anticipated since creatine potassium and phosphorus play a definite role in muscular contraction The amounts of phosphatides of calcium of creatine and of potassium in the hearts of patients with an abnormal or weak myocardium were found to be altered

Abnormalities of this kind may lead to cardiac failure but the evaluation of these findings and the application to the clinic is still remote

Involvement of the Myocardium in Other Diseases

Tumors The heart muscle is frequently invaded by tumors from neighboring organs and in rare cases is the site of primary growths these are discussed briefly in connection with pericardial new growths

Sarcoidosis Death from cardiac failure is not unusual in sarcoidosis (Boeck s sarcoid Schaumann s disease) While a detailed description of this disease is beyond the scope of the present book attention may be directed to a few clinical features all of which although common are rarely present in a single case

The superficial lymph nodes are often enlarged and the skin may show a variety of lesions (lupus pernio of Besnier) The pulmonary infiltrations and enlargement of the mediastinal lymph nodes closely simulate the involvement of tuberculosis Focal destruction of bone occurs in the distal parts of the extremitie Iridocyclitis is often combined with enlargement of the parotid gland and fever The red blood cells are hypochromic the sedimentation rate is increased and occasionally an eosinophilia or monocytosis dominates the blood picture If superficial glands are involved biopsy of the firm grey noncaseating nodules which may reach 1 cm in diameter will disclose tubercle like granulomas composed of epithelioid and giant cells of a foreign body type

The etiology of this disease is unknown nonspecific allergy is suspected to exist but has not been proved Many arguments speak in favor of a tuberculous origin While it affects the white and black races the vast majority of American cases have been in Negroes The course has an insidious onset and is characterized

by a slow advance that may be punctuated by remissions or recovery Bundle branch block and atrioventricular block are common Death occurs usually from heart failure although cardiac clinical manifestations stand in the background until the disease is far advanced

Sickle Cell Disease Another disease associated with cardiac hypertrophy and chronic cardiac failure is sickle cell anemia If as often happens the patient has recurrent attacks of painful joints and a systolic murmur at the apex as well as an enlarged right ventricle involving mainly the outflow tract the erroneous diagnosis of rheumatic heart disease is frequently made Anginal retrosternal pain is not rare Occasionally epistaxis is seen The left atrium may be enlarged but rarely to a marked degree The P R interval may be prolonged The RS T segment is often depressed and the T waves are abnormal This chronic hereditary familial disease is confined almost exclusively to Negroes Apart from the sickle cell trait a rather common intrinsic defect of the erythrocyte in Negroes anemia is often present with the red cell count down to 1 000 000 cells Highly characteristic are the punched out ulcers near the ankles which simulate the ulcerations of syphilis Activity of the disease is often reflected in attacks of abdominal pain nausea vomiting and moderate jaundice which may closely mimic an acute abdominal emergency Sometimes the bone changes which consist of peculiar radial striations are highly suggestive

A variety of neurologic manifestations due to thrombosis of different vessels supplying the central nervous system dominates the clinical picture in other cases The combination of anemia thrombosis and jaundice together with the cardiac findings previously mentioned may suggest a subacute bacterial endocarditis although confusion with a rheumatic carditis is more common The cardiac changes are due partly to the occlusion by sickle cells of small vessels in the lesser circuit and partly to a similar process in the coronary arteries The anemia also plays a role

For differential diagnosis from rheumatic fever which may be difficult one should consider the normal sedimentation rate the normal left atrium and the absence of relief from salicylates in sickling disease In this condition the pain is also located more over the bones than over the joints On rare occasions rheumatic heart disease and sickling were seen simultaneously in the same patient

Von Gierke s Disease Another disease characterized frequently by cardiac enlargement and symptoms of heart failure in a child is Von Gierke s disease or glycogen storage disease In the more common hepatic type the liver is greatly enlarged the fasting blood sugar level is low sensitivity to insulin is increased and the elevation of blood sugar following the injection of epinephrine is smaller than normal ketonuria without glycosuria is often in evidence In the cardiac type enlargement of the liver and kidneys may be slight and the fasting hypoglycemia and ketonuria are usually absent Both varieties may be associated with mental retardation and epileptiform seizures The outlook in the cardiac type is very unfavorable and treatment of the heart failure by the usual remedies is unsatisfactory

Idiopathic cardiac hypertrophy that is hypertrophy of the heart without any visible cause comprises a variety of conditions Formerly patients with thiamine deficiency or primary pulmonary hypertension were included and the condition is more rarely diagnosed with advance of our knowledge

The abnormality is found more often in males Increased deposits of glycogen were found in familial types (Evans) In many patients with this syndrome increased fibrosis is found at post mortem so that one of the myocardial diseases of unknown etiology mentioned above have to be assumed In such cases the term idiopathic hypertrophy is not really correct

There are numerous other diseases with cardiac repercussions but in general the alterations of the heart are interesting incidental findings rather than essential features of the process

SYMPTOMS AND SIGNS OF THE MYOCARDIAL DISEASES

Many symptoms and signs specific for myocardial lesions have been mentioned in previous chapters and some of the clinical features of cardiac involvement in tonsillitis diphtheria thiamine deficiency and coronary sclerosis have been reviewed In the present section the chief symptoms and signs common to all myocardial affections will be discussed

Dyspnea If heart failure supervenes dyspnea particularly nocturnal dyspnea occurs in all myocardial lesions for in all of them including coronary sclerosis the left ventricle is predominantly damaged This group includes the great bulk of patients whose nights are made sleepless by Cheyne Stokes respiration Such patients are often treated for asthma with epinephrine and asthma remedies so that a considerable period may elapse before the cardiac disease is recognized

Pulse The peripheral arterial pulse may be rather small if the myocardium is badly damaged It is understandable that the diminution of contractile power of the left ventricle will reduce the stroke volume whenever the myocardium is profoundly injured Naturally a small pulse since it is present only when myocardial failure is advanced is a very unfavorable prognostic sign

Palpation The results of palpation over the cardiac area are meager The left ventricle is chiefly involved and its pulsations are often not felt normally Many patients are advanced in age with the result that the heart is covered by emphysematous lungs Finally a heart with a damaged myocardium reveals weaker pulsations than one with a healthy muscle In some cases however the presence of a heaving apex beat indicates marked hypertrophy of the left ventricle In other patients with pulmonary congestion the closure of the pulmonic valves is palpable If gallop rhythm is present it can often be detected by palpating the chest between the lower end of the sternum and the apical area (see below)

Percussion As pointed out earlier percussion often reveals a heart of normal size despite considerable myocardial damage Later percussion shows (as x ray confirms) an aortic configuration Finally with the development of back pressure in the lesser circuit mitralization appear In this stage even dilatation of the left atrium may be found when the patient is examined in the right oblique

position with the administration of barium to visualize the esophagus If the heart is strikingly large in myocardial disease (cor bovinum) without relative mitral or tricuspid insufficiency being present the existence of hypertension should be suspected even if the blood pressure is normal at the time of examination

The size and shape of the heart in late stages with dilatation to the right and left as well as mitralization closely resemble the picture presented by combined mitral aortic stenosis and tricuspid lesions or the one occasionally seen in pericardial effusions The absence of pulsations along the cardiac border on fluoroscopy in cases with severe myocardial damage strongly suggests the latter

Auscultation Not rarely auscultation yields normal findings Normal pure and loud heart sounds may be heard despite a very advanced myocardial lesion This is the chief reason why the examiner is led astray in those cases in which percussion has not provided satisfactory results Sinus tachycardia is common but bradycardia may also be present

Often soft or distant heart sounds are considered evidence of myocardial disease As a matter of fact the heart sounds may become more distant as the disease progresses and louder with recovery from myocardial damage Usually however there has been no opportunity to examine the patient earlier for comparison so that the discovery of distant heart sounds cannot be unequivocally attributed to myocardial damage Even slight superimposition of the lung over the heart in the precordial area or obesity may make the heart sounds distant Heart sounds are also distant in patients with a markedly convex thorax and a deep position of the heart

Abnormal accentuation of the heart sounds splitting of the first or second heart sound are common findings but they must be interpreted with great care as evidence of myocardial disease such signs may be elicited in young healthy individuals as well as in cases of cardiac neuroses and hyperthyroidism

Often no systolic apical or aortic murmurs are audible When present they should always be regarded with suspicion and must be distinguished from physiologic innocent murmurs Every systolic murmur — those of recent appearance in particular — demands careful examination

When for any reason the left ventricle undergoes a marked dilatation relative mitral insufficiency may appear If the patient is seen when the lesions are fully developed it is often difficult to decide whether he has a relative mitral incompetence or a structural one of rheumatic origin

Not uncommonly great dilatation of the right ventricle causes relative tricuspid insufficiency

Electrocardiogram The electrocardiogram has paramount importance in the diagnosis of myocardial lesions Slurring notching or widening of the QRS complexes abnormalities of the RS T segments and T waves in leads I and II and the chest leads are of great significance In acute isolated myocarditis an elevated PS T segment (as in acute myocardial infarction) has been observed (Gillis and Walters) probably due to patchy necrosis of superficial myocardial fibers

It must be pointed out again that a normal electrocardiogram does not preclude the presence of a severe myocardial lesion moreover repeated tracings must be obtained for the alterations are often transient Therefore in diseases known to have a high incidence of myocardial involvement such as rheumatic fever the electrocardiogram should be recorded frequently but in chronic diseases the interval between tracings may be as long as six months provided the symptoms and signs remain unchanged

Practical experience shows unfortunately that insufficient knowledge of the normal variations of the electrocardiogram very often leads to an unjustified diagnosis of a myocardial lesion Therefore great caution must be observed before a heart muscle is pronounced abnormal on the basis of the electrocardiogram alone

Gallop Rhythm

Gallop rhythm is an extremely important auscultatory sign in myocardial disease It is however ambiguous and should be evaluated only in conjunction with other clinical signs

The first and sometimes difficult task is the distinction between splitting (duplication) of the heart sounds and gallop rhythm This differentiation is usually based on the fact that in gallop rhythm the third sound is separated from the other sounds by an appreciable interval whereas the interval between the two parts of a split sound is extremely brief Thus in cases without prolongation of atrioventricular conduction time the sound caused by the atrial contraction appears very shortly before the first heart sound In some cases however recourse to graphic registration of the heart sounds is necessary in order to differentiate between these phenomena

If less important details and minor differential points are disregarded four types of gallop rhythm should be differentiated (1) Protodiastolic gallop rhythm (2) Presystolic gallop rhythm (3) Summation gallop rhythm (4) Systolic gallop rhythm

(1) PROTODIASTOLIC GALLOP RHYTHM This originates in a mechanism similar to that of the physiologic heart sound and creates a similar impression on the examiner (figure 4) The third heart sound is a very common finding in children and healthy young adults but it disappears in the adult With development of myocardial damage the rush of blood into the atonic left ventricle may cause the third heart sound to appear early in diastole even in adults This is the protodiastolic gallop rhythm The new sound is explained by vibrations of the ventricular wall or the valves (Lewis and Dock) when the ventricle fills the sound is prone to occur when this filling takes place under increased pressure caused by congestion According to other observers protodiastolic gallop rhythm is caused by the impact of the left ventricle on surrounding structures during diastolic filling

Differentiation from a normal third heart sound is impossible by auscultation or graphic registration If an organic heart lesion is present the new sound is presumed to be due to gallop rhythm Some think the differentiation can be accomplished by the following means (Bramwell) the third heart sound cannot be

palpated it is closer to the second sound than is the new sound in gallop and the third heart sound can be heard with a normal rate whereas gallop rhythm is observed usually with increased rates There are cases however particularly in the younger age group in which differentiation is impossible If the patient is over 30 years old a gallop rhythm can usually be safely assumed for a physiologic third heart sound is rare at this age

(2) PRESYSTOLIC GALLOP RHYTHM In this type the new heart sound precedes the two normal heart sounds by an interval which is usually longer than that in a split first sound (figure 45)

It happens however that occasionally this interval is not sufficiently prolonged to permit differentiation without recourse to graphic methods Heart sound registration shows that the new sound is definitely presystolic whereas in mere splitting of the first heart sound it is systolic

The mechanism responsible for this type of gallop rhythm is disputed While many still believe that an audible contraction of the atria is responsible there are strong arguments to support the assumption that its mechanism is similar *to that causing protodiastolic gallop rhythm Considered in this light* the cause would be again found in ventricular filling as affected by atrial systole Thus both types of gallop rhythm would have the same origin If the P R interval is prolonged the atrial contraction occurs earlier in diastole gallop rhythm is then common for a summation takes place (see below)

(3) SUMMATION GALLOP RHYTHM This is the most common form It is heard when the heart rate is accelerated (usually over 100 beats per minute) or with a prolonged P R interval Under these conditions vibrations due to early filling of the ventricle coincide with vibrations created by systole of the atrium and *gallop rhythm appears Thus many times when each factor alone does not suffice* to cause gallop rhythm the combination produces a distinct new heart sound It is clear from this definition that even the physiologic third heart sound often will become intensified or audible with an acceleration of rate owing to this summation factor

This mechanism of summation also makes understandable the findings of those investigators who concluded that *protodiastolic gallop rhythm* is bound to atrial contraction In the patients examined by them a summation gallop existed

*The importance of rate for the appearance of gallop rhythm is easily demon*strated Often a gallop rhythm disappears when a fast rate is slowed by treatment or even temporarily slowed by carotid pressure

(4) SYSTOLIC GALLOP RHYTHM (SYSTOLIC CLICK) This form was described a long time ago by Potain Two types are differentiated The mechanism of one heard best over the apex is unknown The other and more common type is heard at the base of the heart and derives from changes of the tonus of the aorta and pulmonary artery under the systolic impact of blood It has been found in typhoid fever tuberculosis and in nervous individuals It does not seem to be a significant *sign of cardiac disease* but is often confused with diastolic gallop

rhythm Rarely pericardial or pleuropericardial adhesions may cause a similar phenomenon

Frequency In 1353 consecutive cardiac patients gallop rhythm was found in 62 (Bramwell) In 50 of these the heart rate varied between 90 and 120 In 60

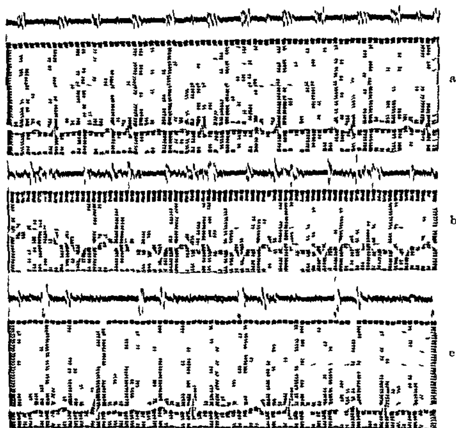


FIG 45 Three instances of gallop rhythm The top tracing (a) shows a gallop rhythm in a patient with coronary sclerosis and myocardial failure The three heart sounds are clearly visible There is a sinus tachycardia a summation gallop developed The middle tracing (b) also shows a summation gallop in a patient with hypertension and marked hypertrophy and dilatation of the left ventricle In the lowermost tracing (c) the P R interval in a patient with coronary sclerosis was prolonged to 0 24 second The first heart sound was dull and shows low vibrations in the stethogram while the second heart sound was accentuated This is an instance of presystolic gallop

cases of gallop rhythm (Wolferth and Margolies) the protodiastolic type was present 14 times the presystolic type 2[illegible] times and a summation gallop 24 times

Clinical Aspects The new sound in gallop rhythm is dull and of low pitch It is heard best over the apex the lower sternum and at a point between these two areas Often it is present only when the patient stands or after light exertion due

to the increase of rate In most patients it is heard better in the supine position It has often been stated especially by the French school that gallop rhythm over the lower sternum develops in the right ventricle whereas the type heard best over the apex originates in the left ventricle While some authorities accept this differentiation it is our experience that very commonly gallop rhythm is detected only over the lower sternum in cases of coronary sclerosis or hypertension in the absence of hepatic or venous engorgement that is in cases of left ventricular damage

Gallop rhythm is frequently palpable The rapid succession of heart sounds creates three impacts resulting in the appearance of a peculiar and characteristic sensation which older workers called tremor cordis

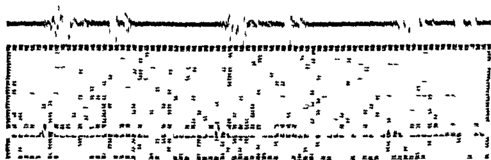


FIG 46 Split second sound in a patient with left bundle branch block (Lead II)

With the appearance of atrial fibrillation and the cessation of effective atrial contractions gallop rhythm often disappears But the assertion that gallop rhythm does not occur during atrial fibrillation is certainly incorrect That type of gallop rhythm which is produced by the flow of blood into the ventricles during the early part of diastole may persist despite fibrillation Only the presystolic and summation types vanish

Differential Diagnosis Mitral stenosis is sometimes difficult to exclude The diastolic apical murmur of mitral stenosis is brief low pitched and mid diastolic often it closely resembles a third heart sound An enlarged left atrium may be present because of left ventricular failure

In cases of continuous bigeminal rhythm caused by extrasystoles occasionally the first sound of the extrasystole alone is heard while the second sound is absent This happens particularly when the extrasystoles are very premature and filling of the ventricle is insufficient systole is then so weak that the semilunar valves are not even opened and no second sound appears In these cases three loud sounds are heard which may cause confusion with gallop rhythm

Clinical Importance Very often gallop rhythm heralds the beginning of myocardial weakness long before other evidence appears It is notably common in cases of myocardial damage and hypertension with an increased heart rate It is however not rare in patients with a normal pressure and a normal or slow rate

Under certain conditions it has no great importance Thus in rheumatic fever the sinus tachycardia and the prolongation of the P R interval may lead to a summation gallop rhythm which does not necessarily indicate myocardial weakness In most cases however gallop rhythm is the 'cry of the heart for help' and suggests the administration of digitalis It is an ominous sign with an acute coronary thrombosis and its importance here is obvious from the fact that among 62 cases observed by Bramwell only 15 survived for more than 18 months

Gallop rhythm is commonly encountered in patients with intraventricular block (bundle branch block arborization block) (White) This finding is apparently coincidental however since gallop rhythm and intraventricular block are both due to myocardial damage Splitting of the second heart sound is common in bundle branch block (figure 46)

Gallop rhythm is rarely discovered by those physicians whose attention has not been specifically drawn to this phenomenon at the time of under or post graduate instruction This finding is more important than the discovery of a murmur Therefore it is important that those charged with the responsibility of instructing medical students make sure that every student becomes familiar with gallop rhythm

Pulsus Alternans

Pulsus alternans is another valuable sign of myocardial weakness and myocardial disease By this term one understands the regular alternation of large and small pulses with rhythmic cardiac actions Accordingly this phenomenon is absent in atrial fibrillation Very often it is absent during regular sinus rhythm but immediately follows extrasystoles for a long or short series of beats (figure 95)

Incidence Among the radial pulse tracings of 300 cardiac and cardiovascular patients pulsus alternans was found in 71 (White) The phenomenon appeared temporarily only after extrasystoles in 55

Diagnosis In outspoken cases it is detected at once by ordinary palpation of the radial artery Every second pulse is smaller In a few cases we have been able to count only half as many pulses in a peripheral artery as heart beats heard by auscultation Thus a patient with 96 rhythmic beats per minute may have a pulse rate of only 48 When pulsus alternans is not immediately obvious by simple palpation it can often be elicited by slight compression of the brachial artery with one hand and simultaneous palpation of the radial pulse in the same arm with the other

Figure 47 shows a pulsus alternans in a pulse tracing (sphygmogram) The simplest method however for discovering a slight pulsus alternans is sphygmomanometry since the stronger beats also provide higher pressure Thus one may find that between the pressure of 150 and 160 mm Hg or between 140 and 160 only alternate beats are transmitted below the cuff (discovered by palpation or auscultation) The height of the diastolic blood pressure also alternates

The phenomenon is often overlooked since in determining the blood pressure the examiner usually does not bother to ascertain whether every beat or every

other beat reaches the periphery just below the upper limit of the systolic blood pressure If however one searches regularly for this phenomenon while taking blood pressure the incidence of pulsus alternans is surprisingly high particularly in a decompensated nondigitalized patient with hypertension Although not uncommon with a normal blood pressure it is then a little more unfavorable from a prognostic standpoint An alternating pulse was found in 33 per cent of decompensated patients

Occasionally the loudness of the second aortic sound or of a systolic murmur likewise varies in intensity with the alternating beats In rare instances alternating cardiac action can be observed fluoroscopically in the form of alternating strong and weak contractions These alternations were recorded by roentgen kymograph (Scherf and Zdansky)



FIG 47 Pulsus alternans

Alternation of waves of the electrocardiogram is usually independent from an alternation of the pulse and is due to abnormal (alternating) spread of the excitation wave over the heart (electric alternans)

To differentiate an alternating pulse from a bigeminal pulse it is important to note that in extrasystoles the smaller pulse wave is usually premature whereas in pulsus alternans it is slightly delayed

The pulsus alternans has been found to disappear or to be greatly diminished when the patient develops congestive heart failure (Ryan et al) This may be connected with the increase of the ventricular diastolic filling pressure in failure

Mechanism Since the original description by Traube and Gaskell many attempts have been made to explain this interesting phenomenon which is easily produced in the experimental animal by poisoning the heart with a great variety of substances

A difference in the excitability of myocardial fibers is generally assumed to be causal The conception of De Boer is at present widely accepted If V represents the whole myocardium and V1 and V2 a smaller and larger part of some what damaged myocardial fibers one may assume that in pulsus alternans the heart contracts according to the formula V—V1 V—V2 V—V1 and so forth In other words with one systole a small part of the myocardium does not participate with the next beat a larger part does not contract Certain observations lead to the assumption that the whole ventricular muscle never contracts

The opinion that pulsus alternans is primarily due to a change of cardiac filling (Wenckebach) has not been completely discarded however an alternans

can be observed in an empty heart or in a muscle strip indicating that the essential factor is probably in the muscle

Significance In a large majority of cases the phenomenon is of serious importance because of its indication of myocardial damage Often it disappears with digitalization Patients presenting it rarely survive for more than a few years after its discovery (Windle) In one patient a distinct pulsus alternans was observed by one of us for seven years that is for two years after the paper by the author (Swildens) was concluded

Pulsus alternans is found in otherwise healthy individuals during an attack of paroxysmal tachycardia with very high ventricular rate Under these circumstances the phenomenon is without significance and vanishes with the disappearance of the tachycardia

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Chapter 14

Diseases of the Pericardium

ISOLATED DISEASE of the pericardium is uncommon but secondary involvement the result of extension of a process from some neighboring organ infection from the blood stream or participation in systemic diseases occurs in a host of di orders Frequently the local pericardial manifestations are submerged in the general symptoms of the primary disease but sometimes they dominate the clinical picture

ANATOMY AND PHYSIOLOGY

The parietal pericardium resembles an asymmetric cone whose apex extends to the aortic arch and whose base is the diaphragm The anterior surface of the pericardium looks somewhat like a right angled triangle since the right side descends almost perpendicularly and the diaphragmatic attachment is more or less horizontal Pleura covers most of the sternocostal surface of the pericardium with the exception of a small uncovered area to the left of the lower sternum Through this triangle of safety pericardiocentesis can be performed without entering the pleura The internal mammary artery is situated 2 5 cm from the left sternal border It escapes injury if paracentesis is performed in the uncovered area at least 3—4 cm to the left of the left sternal border

The parietal pericardium possesses an inner serous and a middle fibrous layer as well as the pericardial connective tissue which unites it to adjacent organs The visceral pericardium is approximately 5—10 microns thick

Since the heart does not entirely fill the pericardial cavity potential spaces exist Normally the cavity contains about 25 ml of viscid fluid whose physio chemical properties approximate those of fluids in other serous lined cavities When a pericardial effusion forms the parietal membrane unfolds and about 150—250 ml the average capacity of the normal adult pericardial cavity can collect in the various pericardial recesses before much pressure is exerted At least this much volume must accumulate before an effusion can be detected by physical examination According to others the diagnosis is often missed if less than 500 ml of fluid are present (Camp and White)

Undue cardiac movements are prevented by the pericardium and its attach ments to nearby structures and to the thoracic cage Alterations of these attach ments may change the configuration of the heart thus descent of the diaphragm pulls on its pericardial attachment and the heart drops when the diaphragm is

elevated by pregnancy or obesity, the heart becomes transverse. The significance of the suspensory function of the pericardium becomes more apparent when external pericardial adhesions angulate or rotate the heart and produce clinical manifestations.

The pericardium also seems to exert a protective influence. The relative rigidity of the fibrous layer is considered an important factor in preventing excessive dilatation of the heart during emergencies. The pericardium is not elastic. Moreover, the pericardium may offer some protection against cardiac infection, for at times inflammations may involve the outer aspect of the pericardium without penetrating the cavity. Pyopericardium is particularly common in patients with pneumonias of the lower lobe of the left lung; this has been accounted for by the relative thinness of the membrane over the left ventricle.

The pericardial serosa is admirably designed to minimize friction during cardiac contractions. If the pericardium is removed surgically, the pleura changes and adapts itself to this function.

Although pericardial diseases are often listed among the painful disorders and special nerve endings can be demonstrated in the membrane, clinical experience teaches that most forms of pericarditis are painless; experimental studies also indicate that the membrane is rather insensitive. Generally speaking, the occurrence of pain in a pericardial disease indicates an involvement of some adjacent structure. Thus, pain in the precordial area, aggravated by inspiration and pressure, is often due to associated anterior mediastinitis. Sharp as well as dull pain in the same area is often noted in an acute myocarditis, which regularly accompanies acute pericarditis. Neck pain is felt when a pleuropericarditis extends to the area of the diaphragm innervated by the phrenic nerve. Dorsal pain is often present if the inflammation involves the tissues of the posterior mediastinum (Capps and Coleman). The pericardium is also relatively insensitive to nonpainful stimuli, such as touch, rubbing, moderate heat, cold, and so forth.

FIBRINOUS PERICARDITIS

Introduction

Pericarditis is the most common disorder of the pericardium; it was present in 3.7 per cent of 36,743 necropsies compiled by the authors. Possibly this is an underestimation of its incidence, since routine microscopic search has not been conducted by many pathologists.

Pericardial inflammation can be classified in a number of ways, for example, according to the etiology or pathology. However, a discussion of each would entail considerable repetition. Thus, streptococci may excite a fibrinous, serous, hemorrhagic or purulent pericarditis. Pyopericardium may be produced by streptococci, staphylococci, pneumococci, etc. For these reasons and in the interest of brevity, it has seemed advisable to select certain general forms of pericarditis for discussion and to amplify these remarks briefly in connection with some important clinical entities.

Acute fibrinous pericarditis pericarditis sicca dry pericarditis may be regarded as the mildest form of pericardial inflammation For cases in which serous fluid collects the term serofibrinous pericarditis is appropriate

Etiology

An enumeration of all possible causes is pointless since any agent capable of irritating the pericardium may be responsible Moreover most of the provocative factors can evoke other forms of pericarditis if the stimulus is more intense

In a vast majority of instances an infection is responsible The coccal infections — pneumo meningo staphylo and gonococcal — are most common Bacillary infection is exemplified by tuberculosis leprosy and more rarely by the typhoid colon group of organisms Higher forms such as actinomyces and even animal parasites (amoeba trichinella and filaria) may also invade the pericardial cavity Pericarditis occurs in trypanosome infection (Rosenbaum et al)

Fibrinous pericarditis is relatively infrequent in subacute bacterial endocarditis in fact the presence of a friction rub has been used as a differential sign between rheumatic carditis and subacute bacterial endocarditis It should be emphasized however that both of the latter conditions often coexist

In many of the exanthemata secondary infection causes pericarditis In some other diseases bacillary dysentery and Asiatic cholera for example dryness of the serosa rather than infection seems responsible for the friction rub since there is no true pericarditis For unknown reasons syphilis of the pericardium is exceedingly uncommon

Several other varieties of fibrinous pericarditis will be discussed elsewhere in this book Traumatic pericarditis is discussed in the chapter on cardiac trauma infarction pericarditis pericarditis over cardiac aneurysms the pericarditis in lupus erythematosus and pericarditis in periarteritis nodosa are discussed in the respective chapters Some of these varieties as well as the pericarditis sometimes seen in Boeck s sarcoid often escape clinical detection

Pericarditis may be excited by some chemical agents In this group belong uremic pericarditis and perhaps pericarditis following coronary occlusion with myocardial infarction The intrapericardial injection of many drugs causes inflammation and has even led to fatal constrictive pericarditis (Beck)

Pericarditis may be induced by physical agents The introduction of small particles of talcum (Thompson and Raisbeck) bone silica and the like into the pericardial cavity causes fibrinous inflammation and the formation of adhesions Likewise foreign bodies (bullets) in the pericardial cavity have occasionally been responsible Neoplasms invading the pericardium may also excite pericarditis Sometimes substances are intentionally placed in the cavity to excite inflammation in the hope that the newly formed blood vessels will provide an additional blood supply for the myocardium

Fibrinous pericarditis may follow roentgen therapy to the chest for hyperthyroidism or Hodgkin s disease and the implantation of radium for carcinoma

of the esophagus The acute mediastino cardiac reaction consists of precordial pain aggravated by movement of the chest fever no significant physical signs but electrocardiographic evidence of pericarditis

Acute pericarditis has been observed in serum sickness (Goldman and Low)

Terminal pericarditis apparently caused by a terminal infection is demonstrable only at necropsy It is neither a clinical nor pathologic entity It is common constituting about 10 per cent of all pericardial diseases Coincident but unrelated cardiovascular disease is present in about 50 per cent of the patients hypertensive cardiovascular disease providing the largest contingent Diabetes mellitus chronic nephritis and neoplasms may also be associated with terminal pericarditis Many other patients have an intrathoracic infection

Pathology

In fibrinous pericarditis the membrane loses its luster becomes rough and feels sandy If the amount of fibrin increases coagulated exudate forms small tufts whose appearance has given rise to many descriptive terms bread and butter heart cor villosum cor hirsutum and the like If the formation of fluid dominates it may contain floccules of fibrin while grossly the membranes show less striking changes Healing is followed by the absorption of exudate by the formation of milk spots or by adhesions between the epicardium and pericardium

The pathology elsewhere depends upon the primary disease In nearly half of the cases an intrathoracic infection (pneumonia empyema pulmonary abscess tuberculosis) will be found Most of the remainder will have some cardiovascular disease (rheumatic fever coronary thrombosis with myocardial infarction nephritis or nephrosclerosis with uremia) A small percentage has an extrathoracic infection or one of the wasting diseases mentioned as being present in terminal pericarditis

Symptoms

As implied above the clinical picture varies in accordance with the associated disease If pericarditis complicates some other infectious disease there may be little to suggest the new complication Sometimes the general symptoms become worse and the fever is somewhat higher or delirium appears in a previously lucid individual Usually however the onset is too insidious to be discerned In some patients with pericarditis the onset may be abrupt with chills fever and local pain

Pure fibrinous pericarditis is often a painless disorder and no distress is felt in uremic pericarditis or in the types associated with many chronic diseases If however neighboring structures are affected — the usual event in the common infectious diseases — there may be pain Thus two thirds of the cases presenting clinically demonstrable rheumatic fibrinous pericarditis and many instances of pericarditis associated with pulmonary infection present retrosternal precordial or left nipple pain This pain may be very intense

The local discomfort which is often described as oppression or tension may receive little attention if the patient is preoccupied with the more obvious general illness While the indefinite precordial sensations contribute to the anxiety they seem too vague for report by the patient In some patients the pain is sticking boring lancinating or constrictive but in others it is dull and heavy If intense it may be accentuated by changes of position local pressure breathing and coughing

Apart from these common variants the distress may be referred mainly to the abdomen and the syndrome may then simulate a ruptured viscus Operations for acute appendicitis have been mistakenly undertaken in children suffering from acute fibrinous pericarditis The dorsal pain is confused with a myositis the pain in the neck or diaphragmatic pain may be equally misleading

If respiration aggravates the distress superficial respiration with inadequate *ventilation may cause cyanosis and dyspnea* Cutaneous hyperesthesia may preclude percussion of the precordium

Signs

If the patient is placed in the proper position and can tolerate the pressure of the hand a fine or rough rub may be palpable This friction fremitus may be biphasic and may follow the apical impulse

The most important diagnostic sign a friction rub on auscultation is absent or eludes detection in over 75 per cent of the cases All gradations are encountered from a mild whisk to rough scraping The rub may be audible over the entire precordium Often it is heard only in a limited region over the area of absolute cardiac dullness for example it may appear only when the patient assume a definite position or in a single phase of respiration

Since the friction sound is provoked by cardiac movements it may be limited to systole or diastole but ordinarily it is heard in both phases When typical the rub is tripartite or appears in four phases (locomotive type) In these instances a rub is audible during diastolic inflow of blood and during systole of the atria as well as the ventricles

The distinction from endocardial murmurs is usually easy for the experienced physician but difficult for the beginner The friction sound tends to be circumscribed to lack a punctum maximum to be transient to change its location and time to lack a sharp association with systole or diastole to sound superficial to present an uniformly monotonous character without a crescendo or decrescendo phase to change during the respiratory cycle and in different positions and to be accentuated by local pressure or by extension of the head Pleuropericardial sounds are rare in the area of absolute cardiac dullness and often vanish during a certain phase of respiration

The friction rub heard over the apical area in patients with marked enlargement of the heart was mentioned on p 60 It is often associated with the large hearts of hypertensives and in children with an old rheumatic heart lesion when the heart approaches the inner surface of the left chest The friction rub limited

to the pulmonary conus in patients with hyperthyroidism is discussed in the appropiate section In all these conditions the friction rub is not due to pericarditis

In some cases of acute pericarditis the skin over the precordium may be edematous The temperature of the skin is often elevated (Elias)

X ray offers no assistance in the diagnosis of fibrinous pericarditis

Electrocardiogram

Knowledge of the electrocardiographic changes is important if confusion with coronary thrombosis is to be avoided The major change is in the RS T segment which is displaced upward or shows a high take off in all leads The QRS complex remains normal The RS T segment may show a curve with its concavity directed upward These changes usually last about one week At this time the PS T segment is found again in the base line and the T waves are bifid disappear or become inverted Ultimately the electrocardio gram reverts to normal provided no other cardiac di ease is present

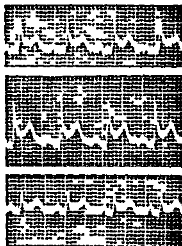


FIG 48 Typical elevation of the RS T segment in acute pericarditis

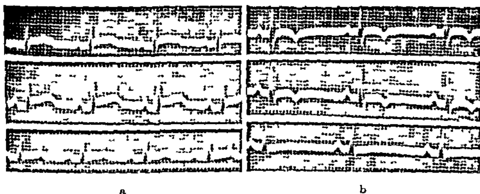


FIG 49 Electrocardiogram of a patient with active rheumatic pericarditis (a) Elevation of the RS T segments at the beginning of the illness (b) typical inversion of the T waves later

The electrocardiogram in figure 48 was obtained from a 16 year old boy with active rheumatic fever and acute rheumatic pericarditis In addition to a sinus tachycardia one sees the marked upward displacement of the RS T segments This change is usually but not invariably most marked in lead II It is caused by

the inflammation of the superficial layers of the myocardium which had already been described by Virchow Experiments show that these changes appear even if a small area of epicardium with the underlying myocardium is damaged in certain places (Boyd and Scherf) The older view according to which these changes were the result of *extensive* alterations of the cardiac surface is incorrect

Figure 49 shows two electrocardiograms from a 35 year old woman with acute rheumatic pericarditis In figure 49 a the high take off' is visible in leads I and II Figure 49 b shows the characteristic next stage with the deeply inverted T waves following a normal RS T segment

Prognosis

Fibrinous pericarditis per se is not a cause of death but the development of this complication in the course of another disease tends to make the outlook more grave

Treatment

Therapy depends upon the nature of the underlying malady

SPECIAL FORMS OF FIBRINOUS PERICARDITIS

Nonspecific Pericarditis

This form also known as acute primary idiopathic benign or indeterminate pericarditis aroused considerable interest in recent years although it has been known for a long time

Nonspecific pericarditis occurs at all ages but is most common in adults It often follows an upper respiratory infection or pneumonia Pain occurring suddenly behind the sternum is a very common manifestation and it may be intermittent It may be aggravated by deep breathing swallowing or torsion of the thorax Sometimes the pain is severe enough to lead to shock In some cases the distress lasts for days The pain may be precordial and interscapular rather than substernal When pain is felt in the abdomen an acute abdominal disease may be simulated Sometimes turning in bed greatly increases the severity of the pain There is some dyspnea and cough moderate fever may persist for weeks The slightly increased sedimentation rate is associated with a mild leukocytosis (up to 10 000 leukocytes) Sometimes differentiation from an acute coronary occlusion is difficult in other patients differentiation from rheumatic pericarditis is necessary

A virus infection was postulated as the etiologic mechanism but this is not established Dressler suggested the possibility that an active rheumatic process is responsible

Roentgenologic examination shows a moderate enlargement of the cardiac shadow which may be the consequence of a pericardial effusion or myocardial damage

For therapy streptomycin chlortetracycline and oxytetracycline have been recommended The prognosis is excellent but the illness can be prolonged because recurrences (acute relapsing pericarditis) are common In recent years beneficial results from therapy with cortisone have been reported Transition of acute nonspecific pericarditis into constrictive pericarditis has been reported (Krook)

Rheumatic Fibrinous Pericarditis

Clinical rheumatic pericarditis may occur at any age but is unusual before the age of 5 and after 30 Most patients are between 8 and 20 years old Pericardial diseases generally speaking are more common in males than in females but no noteworthy differences have been noted in respect to rheumatic pericarditis

The symptoms have been described above but some points merit brief discussion Dyspnea is common and difficult to evaluate since nearly 50 per cent of the patients have an associated valvular disease Palpitation and indigestion may be the predominating symptoms Delirium is unusual in rheumatic fever but occurs in 12 per cent of those with rheumatic fibrinous pericarditis Bradycardia is not rare at the onset and is soon replaced by a tachycardia which may be out of proportion to the temperature The same holds for the very rapid respiration The white blood cell count and the sedimentation rate usually undergo no further increase as the result of pericardial participation in the general disease Serial electrocardiography often shows in addition to the features mentioned above prolongation of conduction time or dropped beats these findings are indicative of the myocardial involvement rather than being proof of a pericarditis

The outlook in children suffering from acute rheumatic fibrinous pericarditis is grave Not a few patients die from this complication while many who survive have some cardiac disability the life expectancy of nearly 25 per cent of those surviving the acute episode is less than five years The presence of an effusion or the presence or absence of a polyarthritis do not seem to affect the outcome Therapy with cortisone and ACTH greatly improves the outlook

An ice bag or cold application to the precordium is generally welcome since it reduces the pain and lessens the sense of palpitation Analgesics such as acetphenetidin may be tried Codeine is very useful since it abolishes the associated distressing cough Usually the salicylates are effective they may be required to render the general situation more tolerable and at times they add to the local comfort The value of any particular agent is difficult to assess since the course of the disease is exceedingly variable Large doses of salicylates particularly in the case of children seem to influence the course of the disease favorably

Uremic Pericarditis

This form of pericarditis originally described by Bright may occur in any disorder associated with azotemia The average age of affected patients is 35 to 37 years uremic pericarditis may be regarded as one of the commonest forms of pericarditis after the age of 30 years Males are affected more often than females

the ratio being 77 to 46. While any chronic renal disorder may be provocative, chronic glomerular nephritis, nephrosclerosis, pyelonephritic contracted kidney and polycystic disease of the kidneys are usually responsible.

The precise mechanism responsible for uremic pericarditis is unknown. Culture of the pericardial fluid yields some organism in nearly 50 per cent of the cases, but the organism varies from case to case; the invasion is due to a terminal infection. The intrapericardial injection of various constituents of the urine, double ureteral ligation and double nephrectomy do not provoke pericarditis. Some investigators believe that a failure of the liver to detoxify certain putrefactive products such as the phenols plays a part; others stress the rather constant association of the pericarditis with necrotic lesions of the myocardium.

Uremic pericarditis is usually asymptomatic, and the diagnosis will often be missed unless a careful search is made for the friction rub whenever this complication is expected. The discovery has prognostic significance — patients usually die within 3 weeks after its appearance, although a few are reported to have survived for two or three months.

The friction rub may be expected in approximately 10 per cent of the patients. At first it is evanescent and faint; then it becomes louder and more persistent, but it may vanish with the appearance of an effusion.

Fall of blood pressure sometimes occurs after the pericarditis becomes manifest. The azotemia, hypertension, persistent acidosis, the tendency to bleed into the skin and mucous membranes, together with the abnormal findings in the urine, make the origin of the pericarditis clear.

Treatment is unsatisfactory and purely symptomatic.

Tuberculous Pericarditis

The tubercle bacillus is capable of exciting all varieties of pericarditis. Reference will be limited here largely to some points of general interest and a few features of the fibrinous form.

Tuberculous pericarditis is not uncommon. It may be expected once in every 100 necropsies in a general hospital and in approximately 4 per cent of all *patients dying from pulmonary tuberculosis. Although the disease occurs at* all ages, it is uncommon before the third year of life. Approximately one third of the patients are less than 15 years old, about one fourth are observed between the ages of 20 and 30, and over one third are observed after the age of 50. It has been estimated that 80 per cent of all cases of pericarditis after the age of 50 are tuberculous. While these figures seem somewhat high to the present writers and seem to neglect the pericarditis following myocardial infarction, they serve to emphasize that tuberculous pericarditis is not uncommon in the older age groups. Males outnumber females in all reported series of cases (about 8? per cent of the cases are men). The disease is more common in Negroes and appears at an earlier age in this race. A history of tuberculosis is often missing.

Pericardial invasion is exceedingly common in the course of miliary tuberculosis and *the incidence of pericardial* involvement is greater than in other

serous membranes The rapidly evolving inflammation affects the epicardium principally and isolated tubercles may be seen along the coronary sulci

In many other cases the infection enters the pericardium by retrograde spread from a mediastinal tuberculous lymphadenitis At times the exact pathway can be followed along a connecting tuberculous lymphangitis Some believe that the subepicardial lymph nodes lying on the anterior surface of the aorta and those at the level of the atria and the peritracheal and peribronchial glands are originally affected so that they may be compared to the retro uterine catch basin in pelvic tuberculosis The existence of primary pericardial tuberculosis is exceedingly dubious

The exudative form is more common than the purely fibrinous one this term embraces serous serofibrinous hemorrhagic and purulent tuberculous pericarditis The incidence diminishes in the order named Often there is only slight inflammation macroscopically and the dominant disturbance is the huge hydropericardium *In other cases the fibrin lies in stratified sheets sometimes with avirulent infections the organized fibrin is converted into a smooth white coat resembling the frosting on a cake*

Another form is called nodular because of the large masses of granulomatous tissue when the nodules are numerous the gross picture may resemble that of a new growth

A rather common variety is termed caseous because a superficial layer of corrugated fibrin and of nonspecific granulomatous tissue covers caseating areas Between the zone of specific and nonspecific inflammation there is often a hemorrhagic effusion

The most common form is adhesive *with partial or complete symphysis of the peri and epicardial membranes Moreover the outer aspect of the pericardium may become adherent to neighboring structures* Sometimes the tissue becomes sclerotic and dense White fibrous tissue compresses the heart producing constriction This type is also called constrictive pericarditis

The clinical picture is so variegated that only general statements can be made In children the onset may be abrupt and difficult to interpret In adults there is often an insidious onset and the few cardiac symptoms are vague nausea vomiting diarrhea palpitation headache and similar symptoms may represent the chief complaints Nocturia eructations and epigastric fullness are mentioned *with some degree of regularity Fever is an important symptom if the patient is aware of it Cough is often present* but ordinarily *is not mentioned unless it* happens to be productive A relatively small number of patients have a sudden hemoptysis or blood streaked sputum owing to the associated pulmonary tuberculosis In a small number of patients night sweats loss of weight dull poorly localized chest pain and precordial distress may suggest the existence of pulmonary tuberculosis

Many patients fail to seek advice *until the chest pain becomes severe* Such pain is aggravated by exertion *or deep breathing* and is *sometimes* associated with blood streaked sputum Exertional dyspnea also often *accounts for* hospi

talization Ultimately the distress becomes constant and a sense of suffocation persists even at rest The ankles may swell the abdomen enlarges and the liver may become palpable so that cardiac failure seems a likely diagnosis This impression is heightened by the pale slightly swollen face A mild tachycardia extrasystoles or atrial fibrillation may be present Often the heart sounds are weak muffled and distant producing a tic tac kind of rhythm The friction rub is usually not heard unless paracentesis has been performed recently

That examination of the lungs frequently fails to disclose any abnormality seems rather surprising since the patient often seeks relief from the sharp stabbing pain in the region of the manubrium the supraclavicular region the neck or shoulder Physical examination discloses no explanation

If there are no suggestive features of tuberculosis in other areas the diagnosis of tuberculous pericarditis may present special difficulties The syndrome makes heart disease probable and only later will tuberculous pericarditis come under consideration This holds particularly for those cases in which dyspnea and weakness progress fever remains irregular or intermittent and evidence of pleural involvement is obtained Many of the symptoms just mentioned naturally belong to the effusion accompanying the pericarditis and are absent if the large effusion fails to develop

Four clinical types of tuberculous pericarditis are described in the aged (1) In the asthenic type the elderly individual rapidly loses weight and strength the evening temperature rises and the ankles may swell Syncope is a late symptom and often a precursor of death (2) In the uremic variety albuminuria hypertension and cardiac enlargement suggest a chronic nephritis if a friction rub happens to be present it is regarded as part of the uremic pericarditis Necropsy reveals a dry somewhat adherent tuberculous pericarditis with renal vascular athero sclerosis (3) In the pleuropulmonary variety dyspnea and cyanosis dominate while clinical examination of the heart reveals nothing abnormal The pulmonary pathology alone seems to explain the picture (4) In the cardiac form progressive dyspnea basal rales hepatomegaly and increasing edema suggest heart failure irregularities of the heart may add to the confusion The course is steadily downward and may be hastened by the development of pulmonary edema or by thrombophlebitis with pulmonary infarction Examination of the lungs fails to disclose an explanation for the dyspnea or cyanosis so that unless a friction rub happens to be present a false diagnosis of myocardial lesion is often made

The average duration of life in acute forms of tuberculous pericarditis with symptoms and signs of effusion formerly was about nine weeks There is a sub acute variety with predominant cardiac symptoms which evolves at a slower tempo — death may be postponed for two years In constrictive pericarditis of tuberculous origin several years may elapse between the onset of symptoms and death There is no doubt however that tuberculous pericarditis may be benign and self limited One wonders how many patients with benign 'virus pericarditis actually have this form

Therapy Great progress has been made in recent years and the mortality has been reduced with the application of streptomycin and isoniazid Thus the management of tuberculous pericarditis is not unlike that of tuberculosis elsewhere in the body

The morbidity and mortality rate is definitely reduced since therapy with isoniazid (or an equivalent agent) and streptomycin became available The ultimate results cannot be evaluated with finality at present but the early results are certainly much better In addition to isoniazid (300 mg daily) and streptomycin (2 grams every third day) some physicians advocate paraamino salicylic acid (12 grams daily)

Operative intervention is warranted in the constrictive type Formerly it was universally agreed that surgery should not be undertaken or if started should be interrupted if evidence of active tuberculosis is discovered With active infections death had been hastened or multiple fistulas formed after operation The situation has changed with the new therapeutic agents (streptomycin isoniazid) and some surgeons recommend pericardiectomy during an active tuberculous pericarditis (Mannix and Dennis) Since adhesions seem to develop much more rapidly under this therapy (Dubourg et al) early surgery in the form of pericardiectomy has been recommended

PERICARDITIS WITH EFFUSION

The diversity of etiologic factors capable of producing pericardial involvement was mentioned in the preceding section the same agents may cause pericarditis with effusion Pericardial effusions without pericarditis will be discussed later

Incidence Pericardial effusion is not rare (2 7 per cent of necropsies) The sexes are equally susceptible until the age of 20 years after which the incidence in females declines A vast majority of pericardial effusions occur before the age of 15 years (95 per cent) and a large number (60 per cent) are said to develop before the age of 5 (Blechmann)

Symptoms The general symptoms of this condition may be greatly modified by the special causative malady but the local symptoms are subject to less variation The speed with which an effusion develops determines part of the symptomatic picture and is also contingent to some extent upon the etiologic agent A rapidly developing effusion may produce signs of great urgency even if the amount of fluid does not exceed a few hundred cubic centimeters whereas a slowly developing effusion may be practically asymptomatic despite a high collection of fluid More than 2000 ml may be found in the pericardial cavity

Fever is usually but not necessarily present The temperature curve depends upon the type and intensity of inflammation and precludes the formulation of definite rules The temperature curve differs in serous and purulent exudates, tuberculous lesions and the like and there are too many exceptions to permit any generalizations

Other symptoms are similar to those seen in fibrinous dry pericarditis Thus pain may appear and may occasionally be of great severity The acute engorgement of the liver may cause pain in the right hypochondrium A large effusion may lead to pulmonary atelectasis and dyspnea

Since the chest wall fails to bulge when the pericardial effusion develops many of the local symptoms can be explained by the space occupying effect of the exudate

Inspection may reveal that the patient instinctively adopts a semirecumbent position often he is apprehensive obviously distressed pale or cyanotic With large effusion the sufferer may sit on the edge of the bed with the left arm elevated on pillows as if to provide extra space the cyanotic face the protruding eyes the cool forehead bathed in sweat the flaring alae nasi the extreme dyspnea and the scarcely palpable pulse paint an unforgettable situation

Bizarre positions were reported in patients with large pericardial effusions Thus the patient may assume the knee chest position or the posture of a praying Mohammedan

Signs Compression of the superior vena cava or the right atrium is common since the thin walled veins and atria must readily yield to high intrapericardial pressure The neck veins may be engorged and may fail to collapse in the upright position or in inspiration Edema of the face neck and upper extremities will be observed in patients with compression of the superior vena cava Inability of the cerebral veins to empty their contents may cause cerebral signs (faintness syncope)

The abdomen may protrude or the bulge may be limited to the upper abdomen when hepatic enlargement is responsible The liver becomes large and hard This event is facilitated by the fact that the wide valveless hepatic veins commonly are subject to direct compression by pericardial effusions owing to the supradiaphragmatic location of their orifices in the inferior vena cava (Elias and Feller) Moreover the liver may give the impression of being greatly enlarged since the pericardial effusion may cause the superior surface of the liver to rotate anteriorly The patients with large effusions and venous compression appear markedly pale in contrast to the somewhat cyanotic hue noted in superior vena caval compression the pericardial effusion diminishes the return of blood to the heart lowers the stroke volume causes the pulse to become small and frequently lowers the blood pressure

Palpation often reveals a small compressible soft pulse The heart rate is usually increased If irregularities are present they are due to the presence of associated myocardial damage The superficial layers of myocardium are always inflamed The apical impulse is often weak or impalpable Cardiac pulsations may be felt however, even in the presence of a large effusion if it develops for the most part posteriorly A friction rub may be palpable despite the collection of considerable pericardial exudate The upper border of the first rib may become palpable this is called the first rib sign of Ewart The findings over the lungs vary

with large effusions which compress or displace the lungs vocal fremitus may disappear from the left paravertebral area

Percussion yields more important information Early the area of relative dullness becomes flat and merges with the area of absolute dullness and the transition from the area of dullness to normal pulmonary resonance may be very distinct Percussion reveals more than the usual dullness found over an enlarged heart There is absolute flatness which is very characteristic and which often permits the diagnosis even of small amounts of fluid when other methods fail to disclose its presence In 1761 Auenbrugger described the percussion sound in pericardial effusions as being completely dead as if percussion were applied to a fleshy limb We cannot stress strongly enough the importance of this sign

At one time great emphasis was placed upon the change in the cardiohepatic angle from acute to obtuse This sign has been proved valueless for x ray examination shows that an acute cardiohepatic angle may be present with all types of effusion

The shape of cardiac dullness varies when pericardial effusion is present If the effusion forms around a heart whose configuration is abnormal owing to some old valvular lesion the pericardial silhouette may retain its configuration Thus a mitralized heart will remain mitralized an aortic heart retains its aortic form (Zdansky) Moderate pericardial effusions often expand cardiac dullness to the right so that the area seems triangular The symmetrical expansion far into the right and left lung fields with the small vascular band on top (figure 51) causes a shadow that has been compared to a Hottentot s hat or to a water bottle the right and left cardiac borders just beneath the vascular band may proceed almost horizontally for a few inches

Dullness in the fifth right intercostal space parasternally so called Rotch s sign is common There is also widening to the left but sometimes this is difficult to determine by percussion when a left pleural effusion coexists In a few patients the diagnosis is suggested by the demonstration of the apical impulse within the area of cardiac dullness ordinarily the apical impulse is the most lateral and caudad point of dullness

Percussion of the posterior aspect of the chest may provide additional information Frequently there is dullness in the lower left posterior chest this has been named the posterior patch of pericardial dullness Frequently this sign is demonstrable in children and may be associated with a small area of tubular breathing and egophony at the angle of the left scapula

In typical cases the heart sounds are faint and muffled however a friction sound may be audible despite the presence of a large effusion when the fluid collects posteriorly and presses the heart near the surface of the chest This also explains why powerful cardiac pulsations may be felt why the sounds and murmurs may be loud and why the classical silent heart is absent Under these conditions confusion of a pericardial and myocardial disease is likely In some instances the pulse vanishes with inspiration (pulsus paradoxus) (see later)

A vast number of additional signs are present in a few cases they owe their origin to pressure upon various neighboring structures Since they are encountered in relatively few patients no detailed description is necessary but a few may be mentioned since they may dominate the clinical picture Dysphagia may be the outstanding symptom when the effusion compresses the esophagus or tormenting cough or hiccough may harass the patient Involvement of the recurrent laryngeal nerve may produce voice changes and pressure upon the sympathetics may inaugurate a number of eye signs

Diagnosis The above account of the physical signs is not intended to suggest that the diagnosis of a pericardial effusion is always easy In about 25 per cent of the cases the friction rub is audible from the start so that the evolution from a fibrinous pericarditis can be followed often the presence of some symptom complex like a tuberculous polyserositis or tuberculous peritonitis will cause the examiner to pay special attention to the heart Under these circumstances little difficulty is encountered On the other hand the effusion may develop insidiously in the course of months or years and subjective complaints are absent or minimal for a long time In these cases the diagnosis may be missed

Not rarely the patient seeks relief from upper abdominal pressure produced by the enlarged liver Pressure on the superior vena cava causes discomfort in the neck and slight dyspnea A suggestion of the correct diagnosis may be furnished when the patient unconsciously adapts the sitting position with slight inclination to the left or forward and the left arm elevated on pillows When the heart is examined the physician may be amazed to discover an enormous increase of cardiac diameters Often the disproportion between the enormous size of the heart and the relatively slight discomfort of the patient leads to the correct diagnosis

Roentgen Examination and Electrocardiogram An x ray film will show the enlargement of the cardiac shadow mentioned before With a simple chest plate an enlargement due to a valvular lesion or a myocardial lesion cannot be not ruled out Thus the form of the heart shadow in figure 50 a which was obtained from a 53 year old man with tuberculous pericarditis is like the one commonly found in a combined rheumatic mitral and aortic valvular lesion or in a patient with hypertension or coronary sclerosis with left ventricular failure and pulmonary congestion Figure 50 b was obtained two weeks later and shows the disappearance of the effusion Pulmonary congestion has also vanished

The more characteristic water bottle appearance of a very large effusion is visible in figure 51 obtained after a paracentesis with the removal of about 400 ml of exudate and the injection of some air into the pericardial cavity This causes a horizontal fluid level and makes the upper left portion of the pericardium visible

On fluoroscopy the complete absence of pulsations at the cardiac borders is often decisive for the diagnosis To be sure in rare instances pulsation of the cardiac borders is not perceptible in extremely severe myocardial damage however in the latter instance the patient displays very obvious evidence of advanced

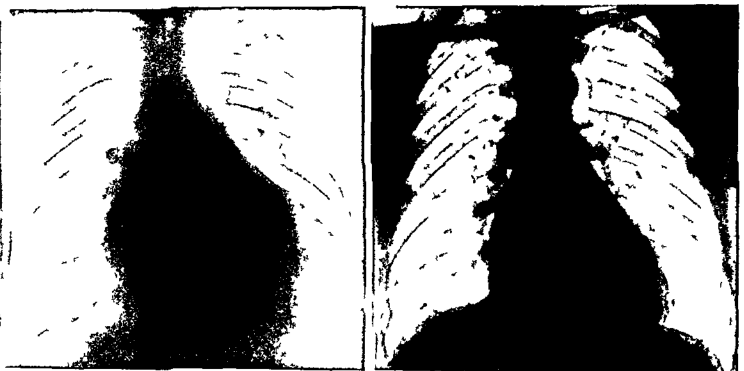


Fig 50 Exudative pericarditis before (a) and following (b) absorption of exudate

decompensation With effusion the still cardiac borders are surrounded by remarkably light lung fields since the stasis occurs back of the heart so that the lungs are free from congestion This does not hold when there is additional failure of the left ventricle for then pulmonary congestion may appear

The diagnostic situation may be complicated by the fact that effusions are sometimes encapsulated If the residual encapsulated exudate is associated with

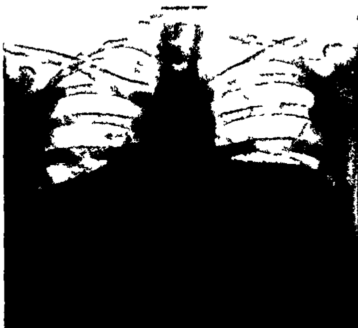


FIG 51 Pneumohydropericardium

low grade persistent inflammation and low pressure a chronic inflammatory pericardial diverticulum may form This encapsulation is prone to occur along the right border of the heart and in contrast to valvular lesions tends to distort the right edge of the cardiac silhouette One may also observe peculiar globular shadows the size of a plum or larger in this area when they are multiple peculiar hexagonal irregular shadows may be visible

Fluoroscopy is more important than films because these loculated effusions often change their shape during the different phases of respiration moreover this method permits the observations of local pulsation in the bulging area The clinical silence of many of these encapsulated effusions is the reason for their belated discovery

Other Tests Angiocardiography may be very useful for establishing the diagnosis The cardiac shadow filled with the opaque agent is seen surrounded by the less opaque shadow caused by the effusion

The electrocardiogram often but not invariably shows low voltage The I and T waves may disappear completely

Great variability prevails in the laboratory findings particularly in respect to the sedimentation rate the white blood cell count and similar findings Whether or not they are altered and if so to what extent depends upon numerous factors indicated in the discussion of the etiology of pericardial effusions

Paracentesis The diagnosis of a pericardial effusion can be established by a test puncture this procedure is not recommended in the presence of an encapsulated effusion because of the increased risk of damaging the myocardium in such cases

Differences of opinion prevail regarding the most suitable place for paracentesis As with puncture of the pleural cavity it is unwise to adhere to inflexible rules The special circumstances of the individual case vitally influence the decision Parasternal puncture should be avoided because of the possibility of injury to the internal mammary artery Generally speaking any paracentesis to the right of the sternum is dangerous since the thin walled atrium may be punctured Paracentesis in the fifth or sixth interspace 6 to 7 cm lateral to the left border of the sternum is recommended With large effusions a site of puncture outside of or below these points may be selected Likewise paracentesis from behind (especially worthy of recommendation for posterior effusion and for simultaneous pleural effusion) and from below (between the xiphoid process and the left costal margin) is often advocated The latter is frequently called the Marfan method

It is advisable to employ local anesthesia (novocaine) It is also advisable to insert the needle detached from the syringe since in this way the resistance of the skin and musculature are appreciated more readily and the entry of the needle into free space is recognized more easily Puncture of the ventricular muscle should be avoided although the dangers of this accident are overemphasized by many The direction of the needle will vary with the site selected for puncture At the place recommended left lateral puncture it is inward backward and upward

The electrocardiogram may be used as an additional safeguard during paracentesis (Bishop et al) When the needle touches the myocardium an elevation of the PS T segment appears in a special lead the needle serving as one electrode

The character of the fluid removed may provide some diagnostic hint of the nature of the process although this information is not always reliable Thus serous fluids are infrequent in infections with pathogenic cocci bloody fluids are often encountered in tuberculous pericarditis and neoplasms Sometimes the provocative microorganism may be recovered but it should be borne in mind that the original organism may be overwhelmed by secondary invaders Apart from the establishment of the diagnosis of an effusion paracentesis has value in eliminating the prospect of a pyopericardium and in lowering intrapericardial pressure

Treatment The management of these patients depends to a great extent upon the etiology Therapy of rheumatic or tuberculous pericarditis has been discussed above

There is justification for the use of sulfonamides in the treatment of pneumococcus pericarditis with effusion since these substances readily diffuse into the pericardial cavity Formerly the oral administration of these drugs was combined with the intrapericardial injection of specific antisera Before much experience was obtained on the value of this combination the use of penicillin gained prominence This method of therapy is indicated in pericarditis evoked by the various pathogenic cocci Broad spectrum antibiotics are also of value There is however the danger that a nonpurulent effusion produced by these organisms may become rapidly converted into a pyopericardium The superiority of surgical intervention over conservative measures in the latter condition makes it necessary to follow the patient very carefully whenever the etiology of the pericardial inflammation suggests the possible development of a pyopericardium As a general rule the situation calls for very careful evaluation of the microorganisms recovered from the pericardial fluid

Apart from these etiotropic measures some comfort may be provided by symptomatic treatment If relief of pain comes under consideration the suggestions made in the section of fibrinous pericarditis are worthy of trial Digitalis and allied preparations are rarely indicated in pericardial effusions and in the absence of cardiac decompensation may act unfavorably

The therapeutic program must also be considered from the standpoint of how quickly the effusion developed If the exudate forms rapidly and causes a marked increase of intrapericardial pressure and severe inflow stasis early puncture and removal of fluid are necessary In large chronic effusions in which the inflammatory or infectious process stands in the background a more conservative plan may be adopted Occasionally success is obtained by means of a mercurial diuretic in combination with ammonium chloride at times a jolt with theophyllin may bring about absorption of the effusion Frequently however these measures are of no avail and paracentesis must be resorted to

It should be emphasized that the quick removal of a large amount of pericardial fluid may be associated with danger If the heart has been subjected to the pressure of the effusion for a long time and if the myocardium has been injured by the accompanying myocarditis and the compression rapid release of the pressure and the acute increase of demands on the heart by the suddenly heightened influx of blood may result in acute cardiac dilatation syncope and the manifestations of severe failure which at times may be fatal The distended pericardium cannot like the normal pericardium prevent excessive cardiac dilatation For these reasons we advocate the use of a 20 ml syringe for the removal of large effusions and slow withdrawal of the fluid Each time the syringe is disconnected for emptying 10 ml of air are reinjected through the needle to prevent an acute reduction of pressure In rheumatic pericarditis it is often well to postpone paracentesis in the absence of definite indications for fairly large effusions are often absorbed in 3 to 4 weeks

In many forms of effusion the relief afforded by pericardial paracentesis is only transient as the fluid rapidly reforms Moreover the effusion may be ab

sorbed very slowly and the clinical picture may gradually change from one of effusion to that of pericardial adhesions Very often the myocardium has suffered permanent damage and cardiac failure ultimately develops Various operative procedures the drainage of pericardial fluid into the pleural cavity or pericardiectomy have been suggested but have not found widespread adoption

The situation may be further complicated particularly in patients with tuberculosis by the development of a polyserositis Sometimes these patients present obvious evidence of progressive tuberculosis with effusions into the pericardial pleural and peritoneal cavities — Concato s disease in a strict sense On the other hand pericardial effusion may be minimal or absent while early ascites (ascites praecox) hepatomegaly or recurrent pleural effusion characterize the clinical picture These cases are often called pericarditic pseudocirrhosis or Pick s disease and they are discussed in the chapter on pericardial adhes ons

SUPPURATIVE PERICARDITIS (PYOPERICARDIUM)

Although the symptoms and signs of purulent pericarditis may depend upon pressure effects and thus may resemble those of nonpurulent pericardial effusion it seems advisable to discuss pyopericardium separately in order to emphasize that the toxic and infectious phenomena may dominate the situation while pressure effects stand far in the background

Etiology In general acute purulent pericarditis may be considered a more intense response of the pericardium to the same etiologic agents which cause the forms of pericarditis previously discussed The intensity of the stimulus seems more important than the nature of the pathogenic agent It must be admitted however that rheumatic pericarditis is rarely purulent (Gerke) whereas pneumococcic pericarditis tends to be suppurative in a large number of cases

Purulent pericarditis was exceedingly common during the great pandemic of influenza in 1917—18 in one series of patients 14 5 per cent of individuals dying from pneumonia had pyopericardium (Stone) Bacteriologically proven pyopericardium due to the influenza bacillus is rare but a complicating streptococcic pyopericardium in influenzal pneumonia is very common In most cases of pyopericardium some intrathoracic infection is present usually this is pneumonia with or (rarely) without empyema In 77 of 123 cases of purulent pericarditis there was intrathoracic infection Among these the pneumococcus was provocative in 45 the staphylococcus in 17 and a streptococcus in 3 (Bisgard)

Pericarditis complicating sepsis is usually purulent This is true almost invariably for the pericarditis following peritonsillar abscess A major source of pyopericardium is sepsis associated with osteomyelitis Among 71 cases of acute osteomyelitis 51 came to necropsy and a purulent pericarditis was present in 33 The lungs were affected in 22 and an empyema or pleuritis was present in 10 18 had abscesses of the kidneys (Pyrah and Pain) Puerperal sepsis furnishes a fair number of examples of pyopericardium

Most of the pathogenic cocci are capable of producing purulent pericarditis Apart from purulent pericarditis as a serious incident in the course of pneumo staphylo or streptococcic sepsis some specific diseases may be associated with pyopericardium Gonococcic pericarditis though rare is often purulent and is almost invariably associated with endocarditis of the same origin Meningococcic pericarditis which occurs in a dry as well as a purulent form is more common since patients survive the acute phase because of the use of antibiotics Bacilli are less prone to produce purulent pericardial lesions Thus typhoid pericarditis is actually uncommon and other organisms of the same group (colon paratyphoid salmonella) are rare causes Actinomycosis may produce a typical pericarditis which is often purulent in character Among the higher organisms the amoeba may enter the pericardial cavity In these cases there is usually a fistulous connection to a liver abscess and examination of the chocolate colored pericardial fluid usually reveals a mixed infection

Incidence Pyopericardium is not common a year may pass without a single example being noted in a large hospital The incidence of purulent pericarditis mentioned in the literature depends upon the source of the material If it is stated that purulent pericarditis is twice as common as the combination of all other forms of pericarditis with effusion the indication is that the material from which the statistics were compiled was predominantly surgical

A vast majority of cases are observed in older children and young adults The disease is not common before the age of five and is equally unusual after the age of 25

Pathology The pathologic picture of purulent pericarditis depends to some extent upon the stage of the process An early serofibrinous stage is followed by the formation of fibrino purulent exudate The surface of the membranes becomes cheesy and soft pure odorless pus forms in variable quantities or a hemorrhagic and purulent exudate is found The inner aspect of the pericardium often resembles a purulent granulating wound with a pyogenic membrane Cardiac movements usually preclude the formation of many adhesions although constrictive pericarditis may follow a purulent inflammation Sometimes the pericardial exudate undergoes considerable organization and massive deposits may attain a diameter of several centimeters More often the pericardium is damaged with the result that remarkably large amounts of fluid collect

Symptoms The symptoms vary because of the diversity of etiologic factors Generally there is an acute illness with swinging temperature chills profuse diaphoresis and evidence of toxicity The diagnosis may be missed because the underlying disease may seem adequate to account for the symptoms therefore no search is made for a second disease or a complication Moreover the development of a purulent pericarditis need not change the general symptoms to a great extent Actually the tendency for pericardial suppuration to remain latent is notorious

Signs Inspection does not give much assistance Most patients present signs ordinarily associated with an elevation of temperature but in rare cases the tem

perature may be normal The respiratory rate and dyspnea may be disproportionately great If the volume of pericardial fluid is large the patient may assume a semi recumbent posture Bulging of the precordium is rare even in children

Palpation percussion and auscultation reveal the same findings as in non purulent pericardial effusion The skin over the precordium is often edematous

There are all gradations of symptoms and signs The clinical picture in the patient whose pleural empyema extends to the pericardium will be different from the one in the patient whose purulent pericarditis results from sepsis with hematogenous dissemination of bacteria (e g when osteomyelitis causes a small myocardial abscess which subsequently ruptures into the pericardial cavity) If the effusion is large tamponade may result Under these conditions the neck veins distend the pulse becomes small rapid and irregular and other evidence of cardiac compression develops With small effusions the area of cardiac dullness does not enlarge although slight edema of the chest wall or of the upper thorax may be seen

The disease is recognized most often when the possibility of its existence is constantly borne in mind in the presence of a process capable of producing pyopericardium Since the existing fever leukocytosis and sedimentation rate need not undergo further alteration when purulent pericarditis develops careful repeated examination of the precordial area is of great diagnostic value If the examiner lacks the necessary experience to detect the flatness in the area of cardiac dullness serial x ray films may furnish a guide to the recognition of the malady

Diagnostic pericardiocentesis is considered unjustified by many competent observers Much of the adverse judgment arises from a period when such puncture was employed as a therapeutic rather than a diagnostic measure Pericardial paracentesis in these patients is not entirely devoid of danger although its hazards are frequently overemphasized by its opponents It is true that the passage of a needle through an infected pleural cavity into a sterile pericardial cavity may be costly or conversely that infection of the pleura during paracentesis of a pyopericardium is also possible The production of a myocardial abscess or a cardiac laceration by an infected needle although rare does occur On the other hand the pleura is usually adherent over the site of puncture and pleural empyema seems to be a greater theoretical danger than an actual one However despite these facts we usually perform pericardial paracentesis if there is any doubt about the situation In this connection it must be admitted that sometimes no pus is recovered even though it is actually present moreover the pus obtained may be ascribed to a pleural rather than a pericardial empyema The danger of overlooking a purulent pericarditis is so great that it seems advisable to err on the side of safety and to perform an occasional unnecessary pericardial tap

Course The course of the disease varies remarkably If the tempo is fulminating cardiac tamponade may occur within a few days on the other hand pyopericardium developing in connection with a foreign body in the pericardial cavity or after a shrapnel wound in the lung may appear late Transmission of infection through the pericardium is sometimes slow

Prognosis In the past under medical treatment fatalities amounted to almost 100 per cent After pericardiotomy became popular this figure was lowered to about 42 per cent (Truesdale) Just before the antibiotics became popular the death rate for pneumococcic pyopericardium (37 per cent) streptococcic infections (31—50 per cent) and staphylococcic pyopericardium (25—34 per cent) was still high, at the present time it has however apparently been reduced decidedly although no large statistical series is available for comparison The antibiotics readily pass into the pericardial cavity in effective concentrations Still the death rate remains high in pyopericardium especially if surgery comes too late

Treatment If pericardiocentesis is performed several syringes should be available to evacuate a fairly large amount of fluid in the event pus is present About one half as much air should be reinjected for in addition to the reasons given above the pneumopericardium greatly facilitates the recognition of any encapsulated exudate by x ray and may modify any operative procedure

Pericardiotomy is indicated even with the modern antibiotics in most cases A few hours of delay before operation is permissible in order to make proper preparation of the patient but next to nonrecognition of the disease procrastination remains a very large factor in the fatal outcome Operation is futile if a pleural empyema or encapsulated pericardial pus is overlooked Momentary reflex stoppage of the heart on incision of the pericardium is a rare but extremely serious occurrence It can usually be avoided by the application of novocaine to the membrane before incision

The administration of antibiotics presents no special problems Many such drugs can be applied locally as well as by other routes

GANGRENOUS PERICARDITIS

Etiology The entrance of putrefactive organisms into the pericardial cavity through a penetrating wound or after perforation of a bronchogenic carcinoma may produce necrosis of the pericardium Pyopneumopericardium is a common result

We have seen gangrenous pericarditis follow the perforation of an esophageal traction diverticulum into the pericardium and similar catastrophes after the implantation of radium into an esophageal carcinoma More rarely we have observed a tuberculous cavity of the lung penetrate an adherent pericardium The greatest number of cases however is provided by penetrating wounds of the chest

Pathology Sometimes the parietal pericardium is smooth and shiny but more often it forms a rigid shell which retains its shape after the heart is removed from the cadaver The visceral layer looks as if tiles had been laid in soft cement Frequently a fistula can be found leading to a bronchus and the foul pericardial content may have been largely evacuated in this way

Symptoms and Signs Most clinical features are described under the heading Pneumopericardium

NONINFLAMMATORY PERICARDIAL EFFUSIONS

Hydropericardium (Hydrops Pericardii)

Congestive Heart Failure The moderate increase of pericardial fluid often found at necropsy in congestive heart failure is usually devoid of clinical significance On occasion however for unknown reasons large effusions cause a marked enlargement of the cardiac shadow in some of these cases Usually they respond readily to treatment with diuretics

Beriberi Scurvy Among 64 cases of oriental beriberi Wenckebach noted a pericardial effusion in 62 hydrothorax in 14 and ascites in 9 Stasis and hypertension in the venous circulation as well as low plasma proteins are considered responsible for the transudation of fluid in this disease Myocardial damage is also present

This effusion explains the striking variations in the cardiac size of the affected patients Hydropericardium does not seem to have been noted in the occidental beriberi heart

Other vitamin deficiencies do not seem to produce pericardial disturbances The epidemic pericarditis encountered in war prisoners in 1918 was due to hemopericardium resulting from scurvy and not from an inflammation

Myxedema Another form of hydropericardium of interest to the internist stems from myxedema This form will be described in the section on endocrine diseases There is also a form of hydropericardium in which the pericardial fluid contains large amounts of cholesterol in an otherwise clear fluid It is asserted that despite the absence of other signs of myxedema these patients respond favorably to the administration of thyroid extract Pericardiectomy has also been recommended (Creech et al)

Pericardial fluids with a high content of cholesterol are also found in tuberculous pericarditis with effusion but under these conditions the fluid is opaque and often chocolate colored

In rare cases we have seen a large transudate in the pericardial cavity of otherwise fully compensated patients without any detectable etiology

Hemopericardium

Individual causes of hemopericardium are mentioned in several places in the present book but may be summarized briefly at this time The normal heart may be ruptured by a crushing thoracic injury or by a fall from a great height this is frequently observed in fatal airplane crashes Rupture of a diseased heart is not a rare event after coronary thrombosis with myocardial infarction In recent years perforation of the atrium by an extension of a bronchogenic carcinoma has been observed with increasing frequency

Fatal cardiac tamponade has been observed after sternal puncture

Rupture of the intrapericardial part of the normal aorta occurs in aviation catastrophes and is sometimes seen in steering wheel accidents when an automobile driver is thrown forcibly against the steering wheel A l

developed in a 23 year old man who received a severe blow on the chest during a foot ball game Four and one half pints of blood were removed and the patient recovered

The pathologic aorta often ruptures in aneurysms when the intrapericardial portion of the thoracic aorta is affected Dissecting aneurysm associated with media necrosis is likewise a common cause A normal coronary artery may be perforated in a stab wound similar accidents have happened during paracentesis or intracardiac injections In a vast number of instances an atherosclerotic coronary artery ruptures into the myocardium rather than into the pericardial cavity Aneurysms of the coronary artery are uncommon they occur in the form of congenital miliary aneurysms as well as in periarteritis nodosa Injuries and rupture of the pulmonary artery with leakage into the pericardial cavity are relatively rare however hemopericardium may follow stab wounds of the vessel

Hemopericardium may result from capillary bleeding in scurvy nephritis acute leukemia and many other diseases of the blood forming organs

Hemorrhagic pericarditis is a term employed to describe rather intense pericardial reactions to an inflammatory stimulus Ordinarily it represents a more severe reaction than serofibrinous pericarditis and its etiology is equally diversified

Pericardial tumors are rare (see below) but a times they produce hemopericardium

The symptoms and signs of hemopericardium depend upon the etiology the speed with which bleeding occurs the amount of blood which escapes into the pericardial cavity and the presence or absence of cardiac tamponade Uninfected blood in the pericardial cavity is absorbed with considerable speed whereas infected blood is rapidly converted into a purulent liquid

Chylopericardium

True chylopericardium is exceedingly uncommon but pseudochylous effusions are frequently encountered in the pericardial cavity We have noted chylopericardium in conjunction with injuries of the thoracic duct Granuloma and new growths involving the duct may also be responsible Experimental chylopericardium can be produced in some animals by ligation of the superior vena cava but it fails to appear after thrombotic occlusion of the same vessel in man

Even more rare is *cholopericardium* the appearance of bile in the pericardial cavity (perforated liver abscess)

Pneumopericardium

Etiology Uncomplicated pneumopericardium is practically unknown for the entrance of air into the pericardial cavity is almost invariably associated with the appearance of blood or some other fluid mixed forms rather than pure forms of pyo hemo pneumopericardium occur

The greatest single etiologic factor is trauma (James) In addition to injury in the usual sen e (contu ion of the chest wall with and without fractures pene

tration of the chest wall by foreign bodies wounds) air may enter via a perforated esophagus (splinter of bone fish bone for example) We saw pneumopericardium in a patient who swallowed his dentures They were found in the middle of the esophagus The penetration of a tuberculous pulmonary cavity or inflammation arising in a tuberculous lymphadenitis or a bronchogenic carcinoma repre ent other mechanisms Equally common however though often unappreciated is the pneumopericardium which follows attempted pleural paracentesis for the induc tion of pneumothorax Pneumopericardium may follow tracheotomy or pneumo mediastinum

Clinical Picture The manifestations are variable as might be expected from the multiplicity of etiologic factors The speed with which air enters is a factor in the production of symptoms a tension pneumotamponade may create symp toms whereas a larger but open wound may avert a rise of intrapericardial pressure

Ordinarily inspection reveals little unle s the trauma or some other releasing factor produces the symptoms of shock Larger collections of air may cause dyspnea tachycardia and sharp precordial pain but small amounts may not even cause engorgement of the jugular veins Palpation is likewise often uninform ative Obliteration of the apical impulse is commonly reported Percu sion may yield a tympanitic or metallic note in place of cardiac dullness or flatness The metallic component of the sound is important since it excludes mediastinal emphysema as the provocative factor This tympany may be difficult to detect when it merges imperceptibly with the surrounding resonance of the normal lung Sometimes a classical cracked pot sound (bruit du pot fele) is obtained on percussion

Auscultation yields diagnostic information A splashing ringing metallic sound synchronous with the heart is audible This continuous Hippocratic succus sion sound is heard in approximately half of the cases The preci e characteristics of these sounds will depend upon the amount of air and fluid present the size of the fistulous opening pericardial tension etc

The mill or water wheel murmur (bruit de roue hydraulique) is almost pathogno monic This sound is difficult to describe and is usually compared to that of a churn It may be louder on in piration than on expiration and may vary in inten sity from time to time for no apparent reason Stokes de cribed the phenomenon as a large crepitating and a gurgling sound to which was added a distinct metallic character Often there is a loud tinkling synchronous with the heart sounds which can also be heard at a distance from the patient The heart sounds as well as the friction rub if present have a metallic character

The clear gas filled space demonstrable around the cardiac shadow and the surrounding bands of pericardium create an unmistakable x ray picture The upper level of the pericardial effu ion is clearly demarcated by air The thickness of the pericardium is easily estimated If a productive tuberculosis is responsible for the accident the pericardium is visible as a den e ligamentous curved band on each side just above the pericardial effu ion

Differential Diagnosis The principal difficulty lies in excluding pneumomediastinum In addition to the distinguishing signs mentioned above metallic tinkle is important since this is usually absent in pneumomediastinum Subcutaneous emphysema is often but not invariably present in pneumomediastinum Fine crackling sounds synchronous with cardiac movements are also suggestive of pneumomediastinum

In patients with pneumothorax the mediastinal pleura may assume the appearance of an arc and may resemble a pneumopericardium Usually the extremely active movements of the heart so typical of pneumopericardium under the fluoroscope are absent

Prognosis Most of the patients recover All forms of pneumopericardium which became secondarily infected were associated with a poor prognosis before the antibiotic era

Treatment Simple collections of air are rapidly absorbed although the patient must be watched carefully If air causes tamponade paracentesis should be performed this applies in all forms of tension pneumotamponade If the air and fluid reform surgical intervention is usually necessary

PERICARDIAL ADHESIONS

The epicardium and pericardium may adhere to each other or the outer aspect of the pericardium may become adherent to neighboring structures as the result of acute or chronic pericarditis Since these events may take place in any form of pericardial inflammation in which repair is associated with fibrosis practically all forms of pericarditis may be causal

Nomenclature

Due to the fact that the presenting situation is usually a postinflammatory syndrome rather than an active inflammation the terms concretio cordis and accretio cordis have become popular The phrase adhesive pericarditis should be discarded since in most cases we are not dealing with an active inflammatory process In concretio cordis the epicardium and pericardium become connected all grades exist between the single fibrous strand bridging the pericardial cavity to the complete obliteration of the sac The term accretio cordis on the other hand emphasizes the adherence of the pericardium to the surrounding structures and is used more or less interchangeably with mediastinopericarditis Important too is a particular form of concretio cordis in which the pericardial scar compresses the heart In some progressive cases usually tuberculous in origin the term constrictive pericarditis is justified but in others the inflammatory lesion has long since subsided and the syndrome is due to chronic cardiac compression by the pericardial scar

Incidence Etiology

Pericardial adhesions are found in approximately 5 per cent of routine necropsies about 48 per cent of patients dying from pericarditis have adhesions

The etiology as indicated earlier is extremely diverse For practical purposes one third of the cases are rheumatic in origin but it is rare for the scar of rheumatic pericarditis to produce cicatrices of clinical importance Many of these patients have no evidence of associated valvular disease Pericardial adhesions presented by another third of the cases may be considered tuberculous in origin It has been repeatedly asserted that all instances of chronic cardiac compression by pericardial adhesions are due to tuberculosis This would appear to be correct if the phrase pericardial adhesions is used synonymously with the syndrome about to be described To be sure an occasional instance of this syndrome has followed a pyopericardium of streptococcic origin but it is difficult to overemphasize the importance of tuberculosis in the genesis of symptom producing concretio cordis Its role in the production of mediastinopericarditis is also so great that it scarcely requires discussion In rare cases the pericarditis followed trauma to the chest

Pathology

As indicated above the scar may consist of a band or a plaque or it may completely obliterate the pericardial cavity There is a growing inclination to distinguish the pathologic changes in the constrictive type from those in the nonconstrictive Thus it is stressed that in the constrictive type the pericardium is thicker more dense and tougher for the fibrous tissue has undergone complete hyalinization The closely bound enormously thick individual collagen fibers are swollen structureless of glassy translucent appearance and without internal architecture The fibers are parallel for the most part but they may form interwoven systems of dense whorls Apart from a few linear nuclei outside the hyaline fibers the scar is almost acellular The tissue is strikingly devoid of capillaries although it may contain some large blood vessels

While this picture is present in many cases others have areas of caseous debris residual old hemorrhages spaces formerly filled by collections of cholesterol crystals calcification of various degrees and extent Sometimes the old line of cleavage between the two layers of membrane has been preserved by a small collection of pus Usually no organisms can be demonstrated although they may be recovered by cultures Sometimes tubercles are found

Pathologic Mechanism

The existence of a pericardial adhesion or for that matter of obliteration of the pericardial cavity does not necessarily result in symptoms On the contrary some adhesions at the site of an old myocardial infarction may support the scar and may perhaps provide an important source for a new blood supply Likewise complete adherence of a thin flexible pericardium to the epicardium may not hamper cardiac movements any more than a thin rubber glove restricts the movements of the fingers On the other hand a thickened pericardial callus encircling the heart may prevent diastolic relaxation and emptying of the great veins In the same way adhesions between the pericardium and neighboring structures the anterior chest wall for example may angulate or rotate the heart and thereby

produce symptoms or signs Systole may also be hampered by the adhesions Accordingly no symptom or sign is obligatory in the clinical picture associated with pericardial adhesions rather it is the total impression that is suggestive In the following discussion no attempt will be made to distinguish concretio and accretio cordis clinically since they are usually combined However a brief review of the classical constrictive type may serve as an introduction

Cardiac catheterization has revealed an elevation of arterial pressure in the lesser circuit that disappears after cardiolysis The right ventricle is hypertrophied The right heart pressure patterns are characteristic but not pathognomonic The right atrial pressure curves show an M or W form and the right ventricular curve shows an early dip and a plateau formation because of incomplete diastolic filling Electrokymography shows a flat top pattern Myocarditis or amyloidosis of the heart may lead to similar curves

Since the encircling pericardial scar prevents diastolic relaxation of the heart and the inflow of blood from the superior and inferior vena cava is drastically affected the picture presented is one of congestion affecting the tributaries of the superior and inferior vena cava The engorged neck veins are unable to empty and remain filled even during inspiration The hepatic veins are unable to discharge their contents so that the liver enlarges and ascites appears early Since the myocardial fibers undergo considerable atrophy and diastolic relaxation is greatly reduced the heart tends to be small although the thickness of the callus may make the diameters seem approximately normal on x ray films In most patients there has been no antecedent valvular lesion with the result that no murmurs are heard The heart sounds are often weak causing the precordium to appear as quiet as a church

Symptoms and Signs

Dyspnea is a common symptom and occurs only on exertion Frequently the patient complains of increasing weakness The enlargement of the liver is so insidious that pain in this area is uncommon but a sense of fullness or oppression in the upper abdomen develops sooner or later in most patients Most of those afflicted with constrictive pericardial scars seek relief for noncardiac symptoms and although the situation strongly suggests some form of heart disease strikingly little is found to confirm this impression Superimposed on the diagnostic triad engorgement of the neck veins enlargement of the abdomen and a small rather silent heart there may be a host of signs some of which are mentioned below

Inspection This may reveal some edema of the slightly suffused or cyanotic face The edema as well as the cyanosis often stop abruptly at the neck (Stokes collar) The facial edema is most pronounced in the morning and disappears during the day when the patient is up and the inflow of blood from the head into the heart is facilitated The neck veins are distended and under great tension as shown by measurement of the venous pressure Other veins may not show obvious engorgement although pictures taken by means of infrared photography also reveal dilated cutaneous veins throughout the body

In the past great emphasis has been placed upon abnormal movements in the cardiac and other areas Weakness or absence of the apical impulse was formerly considered an important sign although it is now recognized that the impulse is frequently absent in normal subjects and may persist despite the presence of extensive pericardial adhesions Systolic apical retraction may occur with properly located adhesions a forward movement in the same area may be noted in other patients But both signs also occur without adhesions Among the thoracic movements which have received great attention is Broadbent s sign a systolic retraction produced by adhesions in the left axillary line in the vicinity of the eleventh and twelfth ribs it is supposed to be suggestive of posterior mediastino pericardial adhesions but is in most cases absent Moreover it also occurs in other diseases Suitably located adhesions may produce retractions in other areas usually on the anterior chest wall Often the systolic retraction of the inter spaces over the precordium commonly seen in right ventricular dilatation are confused with those appearing in pericardial adhesions

The upper abdomen usually protrudes owing to the massive enlargement of the liver Sometimes the contrast between the large pear shaped abdomen and the small extremities is striking In other patients edema of the lower extremities is a prominent sign although this is less regular than ascites

Highly suggestive in some patients with fixation of the lower sternum is the reversal of chest movements during respiration when the patient is viewed in profile (Wenckebach) Sometimes the position of the lower sternum in expiration closely approximates the position normally seen in inspiration

Palpation This method of examination does not afford much assistance Rarely compression of the pulmonary artery by a scar causes a supravalvular stenosis and a systolic thrill is palpable occasionally tracheal tug is present

Pulsus Paradoxus Usually the pulse is regular rarely atrial fibrillation complicates pericardial adhesions

There is a periodic inspiratory reduction in the size of the regular pulse called pulsus paradoxus This finding is easily demonstrated with the auscultatory measurement of the blood pressure since the systolic pressure level changes in different phases of respiration Pulsus paradoxus may be noted in a great variety of illnesses and even in healthy people When the clavicle is thrust back the pulse may disappear in the radial artery because of the compression of the sub clavian artery between the clavicle and thoracic cage This is called paradoxical pulse of extrathoracic origin A physiologic phenomenon is the so called dynamic pulsus paradoxus in which the pulse becomes smaller in inspiration and very large at the beginning of expiration because of the retention of large quantities of blood in the lung during inspiration With the beginning of expiration this blood is expelled into the left heart In the paradoxical pulse associated with pericardial adhesions the pulse is smallest in deep inspiration and largest in the pause at the end of expiration because with inspiration fibrotic bands compress the aorta more and more while with expiration this compression diminishes

Figure 52 shows a pulse tracing obtained from a patient with pericardial adhesions The pulse becomes smaller in inspiration and the largest pulse waves are visible at the end of expiration

Venous Pressure Blood Pressure The venous pressure is increased to many times the normal value It is continuously high The arterial blood pressure tends to be lower than normal and the pulse small In an attempt to maintain a normal minute volume there is usually a slight but definite tachycardia

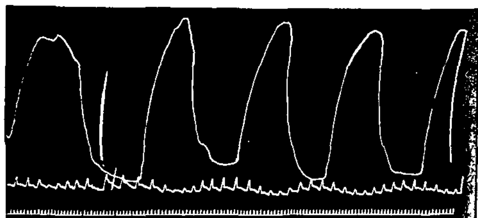


FIG 52 Pulsus paradoxus in a patient with pericardial adhesions

Percussion This may reveal a heart normal in size and shape although some enlargement may be found at necropsy often the heart seems remarkably small

Auscultation Often only pure sounds are found In some cases the heart sounds are dull and split We would consider a duplication of the second heart sound that is frequently heard over the second left interspace as the most common auscultatory finding in patients with pericardial adhesions Occasionally the first heart sound is duplicated at the apex Protodiastolic gallop rhythm appears Mounsey found an early diastolic sound in 18 of 22 patients with pericardial adhesions It appears on the average 0 1 second after the beginning of the second heart sound The abrupt halting of the filling of the right ventricle is apparently responsible

In pleuropericardial adhesions systolic clicks appear (systolic gallop rhythm) probably caused by systolic tension of adhesive bands

Other Signs Palpation of the abdomen reveals the enormous enlargement of the liver Congestive cirrhosis of the liver frequently develops After paracentesis the spleen may also be felt Despite the venous engorgement a caput medusa is remarkably rare When large amounts of fibrin are deposited on the surface of the liver friction fremitus is occasionally noted

Often the legs are edematous this finding may recede after abdominal paracentesis but once it has developed it rarely vanishes entirely Clubbed fingers represent an interesting and not too unusual finding

Roentgen Examination and Electrocardiogram

Roentgen examination often reveals normal findings in a simple obliteration of the pericardial cavity It may add evidence of pleural or pericardial adhesions (tenting at the cardiac borders) and show indications of calcification in the form of radiopaque bands Frequently the cardiac borders are indistinct Fluoroscopy often furnishes suggestive evidence of diminished movement of the cardiac borders and absence of lateral displacement of the heart on change of posture

The electrocardiogram often shows slurring and notching of the QRS complexes and low voltage

Differential Diagnosis

All the symptoms and signs mentioned above may be modified when other conditions are present Thus a left pleural effusion is frequent and polyserositis is not unusual Right pleural effusion is often missing due to pleural adhesions Moreover in accretio cordis the size and shape of the heart may be altered by the presence of some valvular disorder As a rule however the absence of any right sided cardiac enlargement stands in sharp contrast to the massive liver and great venous stasis When the pulmonary artery dilates as the result of increased pressure in the lesser circulation the heart becomes mitralized the adhesions and obstruction to respiration are responsible Slight rotation of the heart may also cause the cardiac waist to disappear These signs in addition to the small pulse and the splitting of the first sound with duplication of the second sound may suggest the erroneous diagnosis of a silent mitral stenosis Such a mistake is understandable since a duplication of the first sound is often audible at the apex whereas the duplication of the second sound is heard best in the second left interspace Sometimes the protodiastolic accessory heart sound is associated with a palpable shock While this is not peculiar to pericardial adhesions it may be unusually distinct when they are present

Course

Patients may be classified into silent types the stationary forms and the slowly progressive variety The first may be asymptomatic throughout life In others a fairly satisfactory equilibrium can be maintained for years particularly when collaterals form and the constriction of the superior or inferior vena cava is relatively slight In the third group chronic passive congestion of the liver sooner or later leads to congestive cirrhosis

Treatment

Since powerful mercurial diuretics and ammonium chloride were introduced a very tolerable state can often be maintained for years Paracentesis for ascites can be almost entirely avoided if the injections are properly spaced formerly the loss of protein as the result of a rapid succession of abdominal tappings soon

created hypoproteinemia and caused marked cachexia Treatment of the heart itself usually can be omitted because this organ is not primarily affected as a matter of fact it is not decompensated at all for the disease is extracardiac

Until recently cardiolysis the resection of the third fourth and fifth ribs in the region of the heart was the method of choice for surgical cases Despite the doubt cast upon the rationale of the procedure the liberation of the heart from cicatrices which angulate or rotate the viscus is often followed by considerable improvement The operation does not seem to help at all in the constrictive variety For this purpose a cautious decortication may be attempted in properly selected cases Sometimes the results are miraculous and health is restored Unfortunately the mortality rate is high (about 20 per cent) This holds particularly for patients with active tuberculosis for the underlying disease is often aggravated by the operation This will certainly change with the wider use of streptomycin and isoniazid Naturally surgical intervention is doomed to fail if the great veins are clamped by adhesions since the constricting cords cannot be severed owing to the danger of incising the vessels

CALCIFICATION OF THE PERICARDIUM

This condition is clinically unimportant since it is not responsible for any complaint or any cardiac failure which may coexist Nevertheless its occurrence possesses some importance because calcification of the pericardium may be regarded as unequivocal evidence of the presence of adhesions

Pericardial calcification formerly considered very uncommon is not an especially rare event and may be expected in approximately 10 per cent of all necropsies for pericarditis (Smith and Willius) It is encountered at all ages and in both sexes It has been reported as early as the sixth year of life and as late as the ninetieth year Males are more often affected than females In 125 cases compiled by one of us 84 were discovered between the ages of 30 and 70

Pericardial calcifications must be differentiated from calcified valves myocardium or mural thrombi (Klason)

Symptoms and Signs A previous history of pericarditis is rarely obtained The most remarkable feature about pericardial calcification is the extent of the deposit and its completely asymptomatic nature If symptoms or signs occur they are not pathognomonic

Pericardial calcification in our experience is most often discovered accidentally usually it is found by chance during a gastrointestinal x ray series since it is seen much more often during fluoroscopy than in the x ray plate of the chest

The calcific deposit assumes a variety of shapes in x ray pictures When typical a crescentic or sickle shaped shadow is observed when the chest is inspected in several planes Frequently the calcium deposit is diffuse and merely confers increased density upon the cardiac shadow Often it is hidden in the abdominal shadow and escapes detection even when a careful search for it is conducted The deposits are found most often along the coronary sulci

Treatment No therapy is required However the presence of a calcium deposit may influence the surgical approach for the relief of cardiac constriction It is extremely dangerous and rather unnecessary to remove calcium plaques over the thin walled atria Moreover plaques over the ventricles sometimes extend into the muscle and an attempt to remove them has been followed by myocardial laceration and cardiac perforation The same situation holds true for plaques surrounding the inferior vena cava lacerations of this vessel during an attempt to remove an encircling plaque has been in our experience an important factor in the unnecessary mortality during pericardiectomy

MALFORMATIONS OF THE PERICARDIUM

Malformations of the pericardium observed in connection with ectopia cordis and monsters have no clinical interest However there are a series of pericardial defects ranging from complete absence of the pericardium to minor lateral foramina near the root of the left lung which are compatible with life

In most cases the defect produces no symptoms and has no effect upon the duration of life Antemortem discovery may be made in the course of an operation for diaphragmatic hernia The diagnostic criteria consist of a greatly increased motility of the heart cardiac hypertrophy without ascertainable cause and displacement of the heart to the left

Among 46 cases compiled by one of us 20 per cent died from pneumonia and 27 per cent had a fresh pleuropericarditis at necropsy Perhaps the absence of a pericardium renders the heart more susceptible to the extension of an infection from neighboring structures

No treatment is required

Diverticulum A true diverticulum of the pericardium is rare Usually it is situated on the right side It depends upon the protrusion of the serosa through a small defect in the tunica fibrosa False diverticula are usually associated with loculated pericardial effusions The diagnosis depends upon the discovery of a round or polygonal shadow of the same density as that of the heart more or less pulsating and resting with a broad base on the right anterior cardiac shadow This unchanging radiologic shadow is unaccompanied by symptoms manifestations if present remain stationary The negative previous history and the latent evolution distinguish the lesion from mediastinal pleurisy and encapsulated effusions of the right interlobar fissure The absence of symptoms tends to exclude aneurysm while the negative findings in adjacent organs eliminate an extension from a bronchogenic carcinoma or some other pulmonary lesion

TUMORS OF THE PERICARDIUM AND HEART

Since tumors of the pericardium and heart often present similar symptoms and signs they may be discussed together at this point Primary tumors of these structures are exceedingly rare but secondary invasion is relatively common Usually both types escape detection even when a careful search is made

Pathology The most common tumor of the heart is myxoma There is some evidence to suggest that many such tumors are actually organized atrial thrombi According to some investigators however we are dealing with a true new growth The diagnosis is possible as Mahaim points out when peripheral emboli of fragments of the myxoma are recognized histologically Typical pictures may be obtained by means of angiocardiography Surgical cure is possible

A large tumor mass in the left atrium will cause symptoms and signs of congestion in the lesser circuit The usual clinical diagnosis as a matter of fact is that of a mitral stenosis particularly when the myxoma (or fibromyxoma) develops on a valve leaflet The mass may even act as a ball thrombus

Lipoma of the heart is rare and there is an intrathoracic lipoma that develops in the anterior mediastinum and projects toward the base of the neck this lipoma is often confused with a cardiac tumor The precise nature of cardiac rhabdomyoma is disputed Bronchogenic carcinoma occasionally invades the heart and may even cause the syndrome of coronary artery occlusion

The most frequent new growth of the pericardium is sarcoma a mixed cell tumor with round and spindle cells predominating Endothelioma is the second most common primary pericardial tumor

Lymburner claims that primary tumors of the heart are found in 0 05 per cent of autopsies Much more common are metastatic tumors from carcinoma of the bronchi stomach prostate breast and esophagus A third group is created by continuous growth of a bronchogenic or esophageal carcinoma into the heart

Symptoms In a fairly large percentage of the cases the symptoms are not suggestive of tumor and are referred to the heart The signs depend upon the size and location of the mass which may produce mediastinal pressure In a subgroup of this type there are terminal symptoms of cardiac embarrassment with acute decompensation ascites rapidly enlarging heart serosanguinous pericardial extravasate and cardiac irregularity Intractable congestive heart failure characterizes the course in many patients causing the erroneous diagnosis of chronic myocardial disease to be made frequently in this group Congestive failure involves the major or lesser circulations Sudden unexpected death is not rare in cases of tumors of the right heart and is explained by a variety of mechanisms any of which may operate in individual cases Metastatic cardiac tumor may occasionally simulate subacute bacterial endocarditis when there are vague cardiac findings and when metastases in the liver and other organs are associated with irregular fever

The early emphasis on the great frequency of heart block in cardiac tumor is due to the rather frequent association of heart block with rhabdomyoma In another subgroup the patient presents a localizing symptom such as pseudo thrombosis of the superior vena cava or compression of a large vessel Constant displacement of the RS T segment in a patient with metastatic tumor of the heart has been described (Rosenbaum et al) Metastatic cardiac tumor is a diagnostic possibility when dyspnea and edema are out of proportion to the known pulmonary metastasis Other patients present evidence of cardiac dysfunction

that cannot be explained Finally a cardiac tumor and particularly a pericardial new growth may present themselves under the guise of a recurrent accumulation of hemorrhagic pericardial or pleural fluid This symptom is not as common as many observers have inferred The discovery of a blood stained pericardial fluid which is not readily explained by some other process has some diagnostic value In most cases neoplastic cells are not demonstrable in the fluid but an increasing number of positive cases are being reported

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Chapter 15

Congenital Cardiovascular Defects

General Remarks

Our knowledge about the congenital heart lesions has increased enormously in the last few years. With the widespread use of angiocardiography and cardiac catheterization, the observation of a large number of patients during cardiac surgery, and the greater opportunity for postmortem examinations, it has been shown that the clinical diagnosis of congenital heart lesions is possible in most instances. The problem is similar to the one that existed more than 30 years ago concerning coronary thrombosis and myocardial infarction. With the discovery of the electrocardiographic signs of that disease, the diagnosis was made more often with simple clinical methods, and today electrocardiography serves in many patients merely to confirm the diagnosis. Similarly, at present cardiac catheterization and angiocardiography are necessary only in a minority of cases unless surgery is contemplated. In most instances the diagnosis is made on physical examination and evaluation of roentgen findings and electrocardiography.

On the following pages only those congenital heart diseases that are seen in patients over 14 years of age will be discussed.

Cardiac Catheterization and Angiocardiography

Cardiac catheterization was discovered by Forssman and used by him and other physicians for clinical research. Such strong opposition arose to the method, however, that it was soon abandoned. It was Forssman himself who introduced uroselectan into the heart with the aid of a catheter, while *O. Klein established measurement of the cardiac output by means of right heart* catheterization according to the Fick principle. This method became widely accepted and employed only after the publication of the studies of Cournand and his co-workers.

Catheterization enables one to measure the pressure in the right atrium and ventricle, as well as in the pulmonary artery.

Normally the pressure in the right atrium varies from minus 4 to plus 4 mm Hg. Average pressures in the right ventricle are 18–25/0 and in the pulmonary artery 25/8 mm Hg. Catheterization also enables us to analyze the oxygen saturation in these parts of the heart and the venae cavae and to introduce opacifying compounds directly into the heart if necessary. The blood flow can

be calculated by using the Fick principle Impacting a catheter in a pulmonary arteriole permits the pressure in the pulmonary capillaries to be measured and that in the left atrium to be calculated In rare cases of septal defects the catheter will be found in the left heart proving by its mere presence the diagnosis of an abnormal direct communication

It is evident that an increased oxygen saturation in the right atrium if compared to the vena cava superior or inferior speaks in favor of an atrial septal defect while an increased saturation in the right ventricle as compared to the other areas will prove the existence of a ventricular septal defect Catheterization is rarely necessary for the diagnosis of a Fallot syndrome or a patent ductus arteriosus

The dangers should not be minimized Trauma to the veins or the endocardium may result in a thrombus and lethal pulmonary embolism air embolism has been observed The mechanical stimulus of the catheter in the ventricle can cause not only arrhythmias but also on rare occasions ventricular fibrillation and death The mortality is about 4 per thousand

For the diagnosis of aortic coarctation translumbar aortography has been performed or a catheter has been inserted into an ulnar or brachial artery and pushed up in the aorta Damage of the aortic wall or the aortic valve has been described so that this method should be used only rarely For the diagnosis of an aortic or mitral valvular lesion evaluation of the degree of the individual lesions or evaluation of the degree of left ventricular failure from the diastolic left ventricular pressure catheterization of the left heart has been developed Transbronchial or percutaneous transthoracic puncture of the left atrium is performed

Angiocardiography causes death in about 2 per cent of the cases and should be performed only to clarify the picture before surgery A second injection is particularly dangerous because of hypersensitivity and the method is especially risky in very cyanotic children Sensitivity tests are of little value A vein is usually exposed and the agent injected in an amount of 50 ml within one or two seconds Local venous thrombosis often occurs

Details of the value of these methods will be discussed in pertinent sections It is most useful in cyanotic lesions with right to left shunt

Other Diagnostic Factors

Circulation Time The determination of the circulation time aids in the diagnosis of some congenital abnormalities namely those with a right to left shunt which permits the injected substance to reach peripheral arteries more quickly than normal The arm to tongue time and the arm to lung time are determined a shunt of appreciable dimensions is assumed to exist when both agree within 2 seconds An arm to tongue time of less than 10 seconds speak in favor of a venous arterial shunt

Clubbing of the fingers or toes can be familial In this case it is often asymmetrical It is unilateral or even limited to one finger if it is caused by a local

disturbance of circulation In hypertrophic osteoarthropathy in congenital heart lesions the proximal bones are involved in addition to the phalanges Hyperplasia and hypertrophy appear in the soft tissues the bones become osteoporotic and patients experience pain More than 60 years ago Bamberger considered an increased peripheral blood flow as an etiologic factor but still little is known about the mechanism

Pulmonary Plethora and Ischemia In addition to the division of congenital heart lesions into cyanotic and acyanotic types they are also classified into those with pulmonary plethora (patent ductus arteriosus transposition atrial and ventricular septal defects) and pulmonary ischemia (pulmonary stenosis Fallot s tetralogy tricuspid atresia)

Cyanosis The depth of cyanosis depends not only upon the degree of the venous arterial shunt but al o on the secondary pulmonary vascular changes and polycythemia

One should be careful not to confuse congenital heart lesions with congenital and acquired forms of methemoglobinemia the latter has been observed in children on a formula made with well water containing a high content of nitrites

Severe cyanosis is seen in transposition of the great vessels actually in children with large hearts and severe cyano is one should consider this ab normality first Here the aorta carries unoxygenated blood and the pulmonary artery returns fully oxygenated blood to the lungs Life is possible only if septal defects or a patent ductus arteriosus coexi t Severe cyanosis also occurs in tricuspid atresia when all blood is shunted from the right into the left atrium It is also seen in Eisenmenger s complex in pulmonary atresia with a riding aorta and septal defect and occasionally in pulmonary arteriovenous fistulas

Slight cyanosis occurs in pulmonary stenosis Fallot s tetralogy some atrial septal defects and in truncus aortae communis In Eisenmenger s syndrome cyanosis appears late (at puberty) In atrial septal defects cyanosis may appear in infants and *children during crying and coughing when the shunt reverses due* to the changes in pressure and the flow goes from right to left

Anoxia Attacks of sudden anoxia are not rare particularly in Fallot s syndrome Morphine (0 5—1 0 mg per 10 pounds of body weight) is useful

Cardiac Pain Cardiac pain is occasionally present owing to hypoxia of the heart muscle It was found in 4 8 per cent of 480 patients with congenital heart disease (Stuckey)

Squatting Taussig pointed out that some children with congenital heart disease e g those with Fallot s tetralogy assume a squatting position The reason is unknown A compression of the abdomen whereby a larger amount of blood is forced back to the heart has been considered a factor

Marfan s Syndrome This abnormality is often found in patients with heart disease One of the most interesting changes is arachnodactyly or spider fingers Patients with this syndrome are often thin and slender with under developed muscles and hyperflexible joints They may have a high arched or cleft palate a pigeon or funnel chest prominent supraorbital ridges large ear

lobes sunken eyes with subluxation of the lens and nystagmus the metacarpal metatarsal and phalangeal bones are abnormally long and the distal parts of the fingers attenuated deformities of the feet and kyphoscoliosis are common Patients look older than they actually are and often have a sad melancholic expression All these signs are rarely present simultaneously in a given patient and there are many abortive cases The syndrome occurs in families In one instance four siblings were affected It has been called dystrophia mesodermalis congenita and is attributed to a general mesenchymal malformation

Congenital abnormalities of the heart or aorta are found in one third to one half of these patients The heart usually shows septal defects while congenital aneurysmal dilatations occur of the aorta or pulmonary artery dissecting aneurysms occur in the aorta the observation of aortic regurgitation has been mentioned in another chapter

Other Syndromes It is estimated that 25 to 50 per cent of the cases of mongolism harbor a congenital heart lesion Of great interest is Kartagener s syndrome which consists of chronic sinusitis bronchiectasis and situs inversus totalis

Etiology

The cause of congenital heart lesions is not entirely clear In the past lues was often suspected as was consanguinity of the parents alcoholism conception in an elderly mother (exhaustion products) or many conceptions at short intervals There is a definite familial tendency

A very important recent discovery throws new light on the problem It has been shown that congenital cataract congenital deafness hare lips cleft palate microcephaly and congenital heart lesions appear in a high percentage of children borne by mothers who had rubella (German measles) in the first three months of pregnancy This early date is important because in an embryo of seven weeks the heart already posses es its permanent shape and the septa are formed Of interest is the observation that the above named abnormalities were observed in mothers who had rubella before conception other observations showed the occurrence of these congenital abnormalities when the mothers had the disease in the eighth or even the ninth month of pregnancy A similar syndrome has been ob erved following infectious mononucleosis According to some investigators this of fection occurs in 90 per cent of cases with German measles while others found it in only 27 per cent It is assumed that the virus passes through the placenta into the fetus the variation in the incidence is understandable since the diagnosis of congenital heart disease is made by some authors solely on the basis of a systolic murmur whereas others use more rigid criteria Possibly as many as 5 per cent of congenital heart lesions may be attributed to rubella or a similar infection but these diseases may be so mild that they can easily be overlooked by both the physician and the patient

Because of the high incidence of eye ear and heart abnormalities following rubella in the early months of pregnancy the interruption of the pregnancy in such cases has been considered An evaluation of this problem has been written

by Wessell While some authors are in favor of an interruption others are not entirely convinced of its necessity

In this connection the experiments of Gilman Gilbert and Spence are highly revealing They injected pregnant female rats with trypan blue which is bound to proteins and alters the plasma proteins In 10 2 per cent of the litter gross congenital abnormalities were found If rats were given a diet deficient in pteroylglutamic acid during the gestation period fetuses showed ventricular septal defects persistent ductus arteriosus and other anomalies (Baird et al) Congenital cardiac anomalies can be seen in rats and mice after x ray irradiation or as a consequence of anoxia

The exposure to radiation either in the form of fluoroscopy or radiography should be limited during the early months of pregnancy X ray radiation anoxia insulin injections and vitamin A deficiency in rats and other experimental animals may lead to congenital heart lesions in the offspring

Secondary Phenomena In patients with congenital heart lesions with and without cyanosis mental retardation is common Growth is also slow Nosebleed and hemoptysis occur and complications such as arterial thrombosis due to polycythemia are observed Marked atherosclerosis develops in the arteries of the lesser circuit Cerebral abscesses either solitary or multiple are not rare particularly when blood reaches the cerebrum without filtration by the lung (they should be treated surgically and with antibiotics)

Further Remarks Owing to the appearance of an abnormality in a developing organ in which the evolution of one part often depends to a great extent upon the proper unfolding of another solitary lesions are less common than combined ones

In embryonic development the heart gradually passes through different stages that closely resemble those of the fish amphibian and bird heart Phylo genesis is repeated in ontogenesis Since the development may stop in any stage the heart (or great vessels) in man occasionally resembles the structures found in lower animals

Congenital heart lesions are not especially uncommon for they are found in more than 1 per cent of routine necropsies Many lesions such as persistent right aortic arch coarctation of the aorta or small defects of the ventricular septum may be recognized late in life and are found accidentally since the patient may feel perfectly well

Owing to the early appearance of some of the changes and the slow development of others and due to the activity of compensatory mechanisms these patients often have surprisingly few complaints This occurs despite the fact that examination of arterial blood reveals a status which would hardly be compatible with life had it developed acutely

Congenital heart lesions have been classified into the cyanotic and acyanotic group Acyanotic lesions are exemplified by coarctation of the aorta most cases of patent ductus arteriosus ventricular and atrial septal defects subaortic stenosis and anomalies of the aortic arch In a large percentage of cases cyanosis is a

late event and often is transient (cyanose tardive late cyanosis) This variety is found in atrial or ventricular septal defects or with patent ductus arteriosus Blood always flows from areas with high pressure to areas with low pressure in the cases mentioned above this is usually from the arterial to the venous side cyanosis is therefore absent If however during decompensation or because of arterial spasm in the lesser circuit pressure increases the flow is from the right atrium right ventricle or pulmonary artery to the corresponding structure in the left heart venous blood will then intermix with arterial blood and cyanosis appears

One of the best known and most common complications of a cardiac malformation is subacute bacterial endocarditis noted in 16 5—19 6 per cent of the cases It seems more frequent in the acyanotic group and is especially common in interventricular septal defects in patent ductus arteriosus and in some asymptomatic lesions like bicuspid aortic valves

The mechanical strain (jet action) at an abnormal location of the endocardium or endothelium of blood vessels is the main reason for infection with streptococcus viridans

So called congenital idiopathic hypertrophy of the heart about which a great deal was formerly written is scarcely diagnosed at present Most cases are now explained by previous myocarditis hypertension in the lesser circuit von Giercke s disease avitaminosis etc Myocardial fibrosis is a common postmortem finding

The electrocardiogram in patients with congenital heart disease rarely has decisive value for the diagnosis In many lesions with augmented strain on the right heart right axis deviation is found In atrial septal defects widening slurring and notching of the QRS complex is very common Sometimes the P waves are higher than normal this happens chiefly in pulmonary stenosis with and without a septal defect

If the congenital heart lesion produces no murmurs differentiation from a cor pulmonale due to pulmonary pathology may be a difficult problem at times

Congenital abnormalities of the coronary arteries will be considered in the next chapter

ATRIAL SEPTAL DEFECTS

Embryology The primitive heart is a simple tube lined with endocardium folds develop in this tube demarcating the various sections Accordingly the primitive atrium is a single structure Early in embryonic life a sickle like fold develops from the upper posterior aspect and passes downward toward the atrioventricular border At the lower border of this fold an opening (the foramen primum) persists temporarily since the septum does not extend sufficiently far In the meantime a gap forms in the primitive atrial septum near its point of origin (the foramen ovale primum) A second fold appears near the original septum and develops more or less as a ring It embraces an oval opening (foramen ovale secundum foramen ovale) Ordinarily the first and second septa fuse and

the foramen ovale secundum closes soon after birth Within the first twelve weeks of life the foramen ovale is closed in 81 per cent of children

The foramen primum type of lesion is often combined with valvular deformities of the mitral valve sometimes a common atrioventricular canal exists The clinical differentiation between the two types is very difficult

Pathology Interatrial communications may be mere slits (probe patency) in the region of the foramen ovale (persistent foramen ovale) This is a very common event and is found in approximately 20 per cent of all necropsies The opening may be 6 to 8 mm in diameter Under ordinary conditions it has no great importance but it may explain some disturbances noted in advanced stages of mitral stenosis or emphysema if pressure in the right atrium rises unduly the foramen is normally closed by a fold This is pushed open by high pressure in the right atrium and marked cyanosis appears due to the right to left shunt

Interatrial communications may also result from a failure of the septum primum to descend normally or because of abnormal regression of the septum primum In these cases the mitral and tricuspid valves often show abnormalities Atrial septal defects are also caused by agenesis of some parts of the septa In this type of septal defect the communication between the two atria may be large In the extreme cases the atrial septum is absent and one speaks of a cor triloculare biventriculare a three chambered heart with one atrium and two ventricles

Incidence Atrial septal defect is one of the most common heart lesions in adults and according to statistics it comprises 7—25 per cent of cardiac malformations In the past it has been frequently overlooked its symptoms being considered clinically the result of a mitral lesion The malformation is more common in women than in men

Pathologic Physiology The flow through the shunt from left to right has been found in some patients to vary from 1 4 to 16 liters per minute The output of the right ventricle per minute may be four times larger than that of the left ventricle In spite of the marked increase of flow through the lesser circuit pressure there need not increase With larger defects there is also at the same time reversed shunt from right to left which causes a fall in the oxygen saturation in the aorta Secondary vascular changes (spasms and later sclerosis) in the lungs increase the pulmonary arterial pressure The greater pressure in the left atrium as compared to the right one is explained by some authors by the greater resistance the thick walled left ventricle offers to the inflow of blood as compared to the thin walled right ventricle

Symptoms The disturbance may exist for many years without symptoms Often evidence of decompensation appears in patients beyond the age of 30 However patients are known who have been active much longer One of our patients is now 72 years old and still active

The signs are usually those of right heart failure i e edema and hepatic enlargement Dyspnea and palpitation occur much earlier but they are moderate Precordial pain may appear

Signs Cyanosis is absent for a long time appearing only when pressure rises in the right atrium and causes the shunt of venous blood in appreciable amounts into the arterial system Cyanosis may also be noted as an intermittent phenomenon for example during bronchopneumonia coughing spells in the newborn or infants or physical exertion with increase of pressure in the right atrium Only in the final stage is cyanosis continuous and deep



FIG 53 Characteristic roentgenogram of a woman with an atrial septal defect

Examination reveals a small peripheral pulse and a systolic or sometimes a diastolic thrill over the pulmonary artery The heart seems mitralized on percussion and there is evidence of dilatation to the right and to a lesser extent to the left A harsh systolic and sometimes a blowing soft diastolic murmur are audible over the pulmonary area The systolic murmur may be soft and may be confused with an insignificant (functional) murmur if the defect is small It appears sometimes after years since following birth the pressure in both atria may be equal The first apical sound is loud The systolic murmur is explained by eddies created in the dilated pulmonary artery with increased flow of blood (mechanism of relative pulmonary stenosis) The diastolic murmur over the same artery was observed in 10 of 53 cases (Bedford et al) whirling of blood caused by the abnormally dilated conus or in the dilated right atrium is assumed to be provocative A relative pulmonary insufficiency is often present (Graham Steell murmur) On the other hand occasionally no murmurs may be heard Furthermore it is characteristic for this lesion to have the murmurs come and go with changes of posture

The second pulmonic sound is accentuated and often split

Roentgen Examination The radiologic signs usually permit the diagnosis The heart is enlarged The prominent arc of the pulmonary artery is typical The



FIG 54 Marked widening of the pulmonary arteries in a patient with an atrial septal defect simulating neoplastic masses in the hilar regions

descent of the main branch of the right pulmonary artery is clearly visible in the right lung field Even its bifurcation into individual branches may be seen The lungs are not congested as is ordinarily seen in a mitral stenosis The left atrium and the aortic knob seem to be small while the right heart is enlarged The pulsations of the pulmonary arteries are accentuated and a real hilar dance occurs The right atrial appendix may be visible on top of the right atrium (Kjellberg et al)

Figure 53 was obtained from a 61 year old woman who complained of shortness of breath on exertion for the past 18 years There was no history of rheumatic fever Figure 53 shows the prominent conus of the pulmonary artery and the large right hilus the main branch of the right pulmonary artery is visible The

heart is enlarged to the right and to the left due to right ventricular dilatation On fluoroscopy hilar dance was pronounced The lung fields are clear The left atrium was enlarged There was no evidence of a mitral lesion

A rough systolic murmur was heard over the pulmonary artery

In some cases a coeur en sabot (Vaquez and Bordet) is found The dilatation of the right ventricle is so marked that this structure forms all but the middle section of the left cardiac border In the border between the right and left ventricle a small sharp edge is visible that gives the impression of a wooden shoe

The shadows of the unusually widened pulmonary artery have been confused with masses caused by bronchogenic carcinoma or Hodgkin s disease (figure 54)

In many cases other congenital abnormalities coexist and may render the diagnosis more difficult The differentiation from some other lesions causing prominence of the pulmonic arc such as ventricular septal defects patent ductus arteriosus or pulmonary stenosis is usually possible but may be difficult at times The features which permit the diagnosis of a persistent common atrioventricular canal in patients with an atrial septal defect are discussed by Wakai et al

Electrocardiography In addition to right ventricular hypertrophy the electrocardiogram shows intraventricular conduction disturbances with slurring and notching of the QRS complexes so that sometimes the picture of right bundle branch block is present Often the P waves are large and rarely the P R interval is prolonged

Catheterization This method permits the diagnosis immediately if the catheter passes through the septal defect and reaches the left atrium and ventricle The oxygen saturation in the right atrium is characteristically greater than in the venae cavae as it is in anomalous pulmonary veins or in ventricular septal defect with tricuspid insufficiency A difference of at least 2 volumes per cent is decisive Slight differences are seen normally This finding is missed when the shunt is reversed from right to left the shunt is often mixed as was discussed above this happens particularly when emphysema or secondary pulmonary vascular changes raise the pressure in the right atrium

Angiocardiography This procedure shows a large right atrium that remains opacified abnormally long because of the shunting of left atrial blood back into it (recirculation) In the left oblique position the shunt may be visible If the above named complications cause a shunt from right to left angiocardiography shows immediate filling of the left atrium

Differential Diagnosis The differentiation of the lesion from an anomalous venous return ventricular septal defect and patent ductus arteriosus is possible in most cases because of the syndromes which will be discussed in the following pages occasionally however the diagnosis is difficult when based on clinical findings alone In pulmonary stenosis the lungs are oligemic Primary pulmonary hypertension is easily confused with this lesion as is a silent isolated mitral stenosis High ventricular septal defect with a communication between the left ventricle and right atrium may be confused with an atrial septal defect on the

basis of catheterization data surgery in such cases may have a fatal outcome (Stahlman et al)

Lutembacher's Syndrome A well known complication is a rheumatic mitral stenosis The combination of an atrial septal defect and mitral stenosis is known as the Lutembacher syndrome In one series of 60 cases of atrial septal defects mitral stenosis was found clinically 12 times Some observers find the combination much more rare and we agree with them Apical diastolic murmurs can be heard in the absence of mitral stenosis when large quantities of blood rush into the ventricle

The diagnosis of Lutembacher's syndrome is easy when the typical prolonged diastolic apical murmurs of mitral stenosis are present It may be impossible in the absence of the murmurs since the symptoms and signs are the same as in an uncomplicated atrial septal defect The left atrium usually does not enlarge presumably owing to the fact that the communication between the atria prevents great congestion in the left atrium and the rise of pressure is transmitted early to the right atrium

It is astonishing that the changes in the heart and therefore in the dynamics are the same irrespective of whether the septal defect is complicated by a mitral stenosis or not It has been pointed out that the flow of blood from the left into the right atrium in atrial septal defects may result from the fact that the left atrium lies cephalad to the right and the septal defect lies in a horizontal plane Thus the arteriovenous shunt may be due simply to gravitational flow

Complications Paradoxical embolism occurs in atrial septal defects and in open foramen ovale Atrial septal defects are the only congenital heart lesions in which atrial fibrillation is common Subacute bacterial endocarditis on the other hand is rare

Prognosis Most of those affected succumb before the fiftieth year Even when a mitral stenosis is present patients may occasionally reach an old age as the case of the oft quoted 74 year old woman shows she had 11 pregnancies and 3 abortions (Firket quoted by Abbott) Pregnancies usually are tolerated well

Surgery Several types of operations have been recommended A plastic button or simple suture has been used (Gross Hufnagel) and many patients have recovered following such intervention Operation is indicated when evidence appears that the load for the right heart is too great A high defect (also called patent ostium secundum) is relatively easily closed Low defects near the valves are closed with difficulty Valvular anomalies are common in such patients The heart is larger and symptoms begin earlier

Bailey et al treated atrial septal defects by atrioseptopexy Ninety per cent of the patients survived the operation with marked clinical improvement when a patent ostium secundum deformity existed However 11 of 16 patients succumbed to surgical correction of an ostium primum One does not operate when a right to left shunt exists

ANOMALOUS PULMONARY VEIN DRAINAGE

This anomaly does not seem to be rare and has become better known only after the wider use of cardiac catheterization The clinical picture is similar to that seen in atrial septal defect In this anomaly one or more of the main pulmonary veins do not empty into the left atrium but into the azygos vein the superior or inferior vena cava or even the coronary sinus vein thus connecting back into the right atrium Often the veins drain into a persistent left vena cava superior If all pulmonary veins drain abnormally a septal defect must exist to be compatible with life and even then these individuals usually die in infancy In the partial form of the anomaly an atrial septal defect may also coexist When less than 50 per cent of the pulmonary venous blood drains into the right atrium cyanosis is absent and patients have been known to reach the age of 80 or more

There are no characteristic findings on physical examination A systolic and rarely also a diastolic murmur may be heard over the base of the heart The second pulmonic sound may be split There is right ventricular hypertrophy and a widened pulmonary artery is seen similar to that observed in atrial septal defects The abnormal hemodynamic mechanism is the same The electrocardiogram shows the same changes as seen in atrial septal defect The differential diagnosis is impossible on clinical grounds but roentgenologic examination is helpful Often one sees ovoid masses in the lung running parallel to the cardiac shadow particularly when a pulmonary vein flows into the vena cava inferior The upper mediastinum shows bulging Snellen and his co workers described a figure of eight mass on the upper cardiac mediastinal area Tomography permits one to follow these abnormal veins and to see their connections which were mentioned above

Often the cardiac catheter is pushed into these abnormal veins and arterialized blood is withdrawn Angiocardiography shows the abnormal veins clearly

Surgical therapy with transplantation of these abnormal veins into the left atrium has been successfully attempted It is a difficult operation If one small vein drains abnormally the portion of the lung from which it comes can be extirpated Even total anomalous pulmonary venous connection has been corrected surgically with success (Burroughs)

PATENT INTERVENTRICULAR SEPTUM

Pathology This congenital defect may appear alone or in combination with other lesions In its pure form it is not as common as generally believed

Uncomplicated *small* patent interventricular septum is often called maladie de Roger after one of the first authors to describe it According to other authors the term Roger s disease should be used only in those cases in which the defect is within the muscular septum We do not see any reason why all pure ventricular septal defects should not be called Roger s disease

In lower muscular defects the murmur is in a lower intercostal space However in a majority of cases (90 per cent) the defect is situated at the membranous

septum (undefended space) Therefore it lies just beneath the aortic valves and communicates with the right ventricle behind the septal cusp of the tricuspid valve Its diameter varies from 0 2–3 cm in most cases The defect develops if the bulbar septum fails to descend properly and does not close the foramen interventriculare in the interventricular septum The defect becomes relatively smaller when the heart grows

Often the opening is very small and only permits the passage of a small probe while in other instances it may be wide enough to admit a thumb If the interventricular septum fails to develop a cor triloculare biatriatum results Children with this condition rarely live beyond the age of four years Acquired *septal defects are discussed in the chapter on coronary thrombosis*

Symptoms Many patients are fully active and free from complaints for many years This happens particularly in those with a small opening when the lesion is often overlooked There are no characteristic symptoms but dyspnea and palpitation may appear in the late stages Fatigue is one of the earliest symptoms

Signs There is no cyanosis for a long time since the blood flows from the left ventricle (with its higher pressure) into the right ventricle In later years complications such as pulmonary emphysema may increase the pressure in the right ventricle so that cyanosis appears at first only on exertion but eventually continuously In large defects the pulmonary resistance is increased very early and a reversed shunt may occur

Physical examination reveals a prolonged systolic thrill over the third or fourth intercostal space to the left of the sternum This is present in only a third of the cases Frequently in the early stages the size of the heart is normal general (right and left ventricular) dilatation may appear later There is no characteristic configuration The pulmonary arc may be prominent and the hilar shadows are increased pulsations of the hilus (hilar dance) may also occur The underdevelopment of the aortic knob may be explained by the fact that much of the output of the left ventricle is lost into the right ventricle As much as 50 per cent of the left ventricular output may be forced into the right ventricle

There is a very loud prolonged harsh rasping systolic murmur with a point of maximum intensity in the third fourth or fifth interspaces to the left of the sternum often it is transmitted to the back This murmur as in other stenotic mechanisms may be louder when the defect is small (figure 55) It may be absent when the same pressures prevail in both ventricles The murmur usually is of steady intensity that is neither crescendo nor decrescendo it may become louder when the patient lies in the left lateral position It may or may not be widely transmitted The second pulmonic sound may be accentuated whereas the second aortic sound is often softer than usual A diastolic apical or pulmonary murmur explained by turbulences and eddies in the left ventricle or pulmonary artery may be heard

Figure 55 shows the stethogram of a child with ventricular septal defect The electrocardiogram is often normal and never characteristic

Patients may reach old age despite the defect Fifty per cent of patients with large septal defects die early in childhood Open heart surgery with extra corporeal circulation now saves many lives

Catheterization and Angiocardiography Cardiac catheterization reveals a high oxygen saturation in the right ventricle this saturation is higher in the upper parts of the right ventricle than in the right atrium Later in the disease if pulmonary resistance and pulmonary pressure rise a right to left shunt occurs and catheterization is of no help It also does not yield sufficiently clear cut data when the opening is small Occasionally the catheter may be pushed into the left ventricle and even into the aorta



FIG 55 Persistent loud murmur filling all systole over the fourth left intercostal space parasternally in an 8 year old child with a ventricular septal defect

Angiocardiography is of no help with small openings With large defects persistent filling or refilling of the right ventricle may be seen An early filling of the left ventricle is only minimal

Differential Diagnosis Differentiation from other congenital cardiac lesions is difficult but is usually possible X ray and fluoroscopy may reveal findings very similar to those in an atrial septal defect (prominent pulmonary arc enlargement of the hilar vessels and hilar dance) The widening of the pulmonary artery and its branches generally is more pronounced in atrial septal defects The systolic murmur in cases of a ventricular septal defect is heard best at a more caudal area it is more prolonged and rougher

If pulmonary pressure rises a relative pulmonary insufficiency may appear The differential diagnosis from pulmonary stenosis may be difficult In this condition the lungs are however oligemic Septal defects can be confused with mitral lesions Differentiation usually is easy by means of the location of the points of maximum intensity and the character of the murmurs

Complications Heart block is an occasional finding This block is usually complete but sometimes only partial Congenital heart block is not necessarily incapacitating and it may occur in the absence of a septal defect Its presence should be expected more constantly than is actually the case since the bundle of His is situated just behind the undefended space Perhaps its rarity may be explained by the fact that the bundle develops before the interventricular septum is

formed Masses of connective tissue often interrupt the path of the atrioventric ular conduction system Since cellular infiltrations of the inflammatory type with excessive growth of connective tissue are commonly found, fetal myocar ditis has occasionally been assumed However the heart block in patients with ventricular septal defects often is not congenital It develops slowly in the first months or years of life because of thickening and development of fibrotic strands at the edges of the defect

Subacute bacterial endocarditis which develops in more than one third of the patients represents a more serious complication The vegetations are usually situated around the interventricular opening in the right ventricle where the blood pressed through the opening impinges on the wall Therefore pulmonary rather than systemic embolism is more common

Surgery Open cardiac operation with the use of a mechanical pump oxy genator is promising and is preferable to the closed methods Sixteen of 20 patients who were operated on survived and there was only one death among the last 13 of the series (Duane et al) The operation was successful in some patients despite the presence of pulmonary hypertension and the presence of a right to left shunt associated with the left to right shunt

PULMONARY STENOSIS

Pathology Incidence Like congenital aortic stenosis pulmonary stenosis with normal aortic root may involve the infundibulum (conus) the orifice itself or the supravalvular part of the artery The degree of stenosis varies widely The opening of the valves may amount to only a few millimeters Sometimes a dome shaped funnel projects into the pulmonary artery Isolated pulmonary stenosis is usually valvular The main right or left pulmonary artery may be absent with a greatly diminished vascularity of one lung

Pulmonary stenosis is more common than was assumed in the past Often it has not been recognized Not rarely the pulmonary valves are bicuspid

Uncomplicated stenosis of the pulmonary artery is compatible with long life — patients may live to the age of 60 years or more In combination with a ventricular septal defect the lesion is one of the more common congenital anoma lies Widening of the area just beneath the stenosis is likewise a common finding as is dilatation of the pulmonary artery beyond an incomplete stenosis In patients with an infundibular stenosis an additional (third) ventricle may seem to be present above the stenosis In instances of a pronounced stenosis of the pulmonary orifice the left ventricle may seem smaller than normal

Symptoms Patients complain of dyspnea fatigue and weakness anginal pain and syncope Often however complaints appear late in life since a slight reduction of the pulmonary circulation will not cause oxygen unsaturation and cyanosis When there is a marked decrease of oxygen saturation squatting occurs

Signs There is evidence of right ventricular hypertrophy on palpation Usually a loud systolic murmur is audible over the pulmonary ostium unless there is a complete atresia It is often accompanied by a thrill The second pul

monic sound may be absent or weak but in some cases particularly in those with a stenosis of the supravalvular type it is loud As in aortic stenosis the systolic murmur may be diamond shaped in the stethogram (figure 56) It is often heard over the back and is often late systolic If there is infundibular stenosis the murmur is heard lower in the third or fourth intercostal space

Occasionally a diastolic murmur is also heard since owing to malformation or a relative type of regurgitation the pulmonic valves are incompetent It is remarkable that this murmur is not heard more regularly with a stenosis of the orifice itself for complete closure of the valves in diastole should be impossible in most cases of stenosis However in a similar way the diastolic murmur of an aortic insufficiency is often absent in an advanced aortic stenosis of rheumatic or arteriosclerotic origin The second pulmonic sound is soft or absent

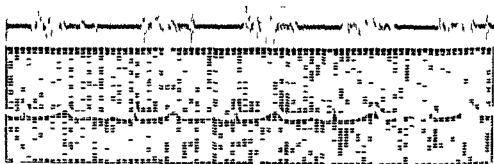


FIG 56 Diamond shaped murmur over the second left intercostal space parasternally in a patient with pulmonary stenosis

X ray examination reveals in patients with an incomplete stenosis of the pulmonary valves a widening of the supravalvular portion of the pulmonary artery that is missing in infundibular stenosis This is explained in a similar way as the widening of the aorta above an aortic stenosis The lungs are oligemic they are however normally vascularized when the stenosis is mild The pulmonary vessels are small

The electrocardiogram shows large P waves and marked right ventricular hypertrophy The T waves are inverted in V 1 and V 2

Catheterization This shows a typical finding The blood pressure in the right ventricle is high and it suddenly falls when the catheter reaches the pulmonary artery The lowest pressure gradient is 10 to 15 mm Hg The oxygen saturation is the same everywhere Figure 57 shows the sudden fall of pressure when the catheter leaves the right ventricle and reaches the pulmonary artery in a 42 year old man with an asymptomatic pulmonary stenosis

Angiocardiography There is dilatation of the right atrium and ventricle The stenosis is sometimes visible (20 per cent) but the picture is often misleading Not much is gained by this test

Not rarely the high pressure in the right atrium forces the foramen ovale open and marked cyanosis appears suddenly because of a marked right to left shunt With an open foramen ovale the left atrium fills early The combination of pulmonary stenosis and open foramen ovale is known as the trilogy of Fallot

Differential Diagnosis In pure cases the differentiation from ventricular septal defect is usually easy because in pulmonary stenosis the point of maximum intensity of the systolic murmur is located higher (in the second intercostal space) But sometimes it may be sufficiently low to cause confusion The loud systolic murmur over the pulmonary area in atrial septal defects combined with

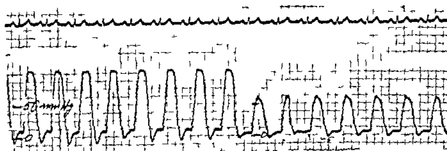


Fig 57 Forty two year old man with pulmonary stenosis (see figure 56) The pressure falls suddenly and appreciably when the catheter is moved from the right ventricle into the pulmonary artery

a prominent pulmonary arc may also cause mistakes Under these circumstances the frequent absence of the second pulmonic sound in pulmonary stenosis may help In pulmonary stenosis the lungs are oligemic One must also distinguish the lesion from Fallot s tetralogy and Ebstein s disease

Complications More often than in any other congenital cardiac disease pulmonary tuberculosis develops due to the abnormal blood supply to the lungs This is somewhat puzzling since the circulation in the bronchial arteries is not directly reduced Soulie et al found that pulmonary tuberculosis was 3 to 4 times as common in patients with diminished blood flow to the lungs as in the general population Moreover the evolution of the illness was more acute

Surgery Mild stenosis of the pulmonary orifice is not treated surgically Patients may live to the age of 75 years In advanced infundibular stenosis resection and dilatation is done (Brock) The operation is best performed when the patient is between the ages of 5 and 12 years Danger increases in older individuals The mortality averages about 10 per cent Campbell and Brock report only 3 deaths in 52 consecutive operations The vast majority of those who survive showed improvement The approach in Brock s operation is from the right ventricle

EISENMENGER'S SYNDROME

In Eisenmenger's triad or complex a large high interventricular septal defect exists causing the aorta to ride over both ventricles There is marked right ventricular hypertrophy and no pulmonary stenosis It has been pointed out recently that separation of a large ventricular septal defect from Eisenmenger's syndrome seems impossible clinically and even morphologically Symptoms and signs are those of a large ventricular septal defect in which a riding aorta must be present

Cyanosis appears late in these patients since the shunt is initially from the left ventricle to the right one However secondary changes in the pulmonary vessels raise the blood pressure in the lesser circuit to a degree that the shunt becomes reversed that is from right to left Sometimes the pressure in the lesser circuit may approximate that in the systemic circulation In these cases the right ventricle may be markedly dilated and signs of right ventricular hypertrophy appear in the electrocardiogram

The roentgenologic signs are those discussed earlier in connection with ventricular septal defects

Catheterization shows an increased pressure in the right ventricle and the pulmonary artery plus the other findings listed in the preceding chapter Roentgen examination and catheterization permit the exclusion of a pulmonary stenosis and therefore a tetralogy of Fallot Angiocardiography shows simultaneous filling of pulmonary artery and aorta It is difficult to differentiate the lesion from essential pulmonary hypertension

There is no surgical therapy

TETRALOGY OF FALLOT

Incidence Pathology This syndrome is found in 75 per cent of adults with congenital heart disease exhibiting clubbing of the fingers and cyanosis Actually it consists of only two defects First there is a pulmonary stenosis which is most often infundibular and in a small minority of the cases valvular Second there is a very large interventricular septal defect which as discussed in the preceding section gives the picture of a riding aorta With the pulmonary stenosis varying from so slight a form that separation from Eisenmenger's triad is impossible to complete atresia and with variations of the size of the ventricular septal defect countless variations are seen Often the foramen ovale is patent

Sometimes a patent ductus arteriosus coexists and makes the diagnosis more difficult Then cyanosis may be absent Large anastomoses exist between the bronchial and pulmonary arteries In cases with pulmonary atresia often the lungs are supplied only by the bronchial arteries A persistent right aortic arch is found in 20 per cent of the cases

Symptoms and Signs Cyanosis appears at birth or after a few years since the pulmonary stenosis raises the pressure in the right ventricle leading to a right to left shunt Squatting is said to be very characteristic (Taussig) Poly

cythemia is marked There is stunting of growth Attacks of unconsciousness occur Brain abscesses are a not infrequent complication

The heart is often a little enlarged and boot shaped (coeur en sabot) and the right ventricle forms a large part of the left cardiac border The lungs are oligemic and the hili are small The concavity in the area of the cardiac waist is conspicuous owing to the absence of a pulmonary conus and a small pulmonary artery The second aortic sound may be loud over the pulmonary area The second sound is not split A systolic murmur and thrill may be found over the base of the heart Often these are absent since the pulmonary orifice is atretic and the riding aorta with a large ventricular septal defect does not cause murmurs The aortic arch is often on the right side this is an important finding if surgery is contemplated The bronchial arteries are enlarged

Laboratory Findings The electrocardiogram shows large P waves in all standard leads particularly in lead II Right axis deviation and signs of right ventricular hypertrophy are common The P waves are very large in V1

With angiocardiography the pulmonary artery and aorta fill simultaneously with the dye The picture of the upper left cardiac border will vary in complete pulmonary atresia and in moderate stenosis In rare cases the degree of pulmonary stenosis can be ascertained In the left oblique position the aorta may be seen originating from the right ventricle

With cardiac catheterization the tip of the catheter may be found in the aorta *Pressure in the right ventricle may reach values of 100/5 mm Hg* The pressure in the pulmonary artery has been found low in those subjects in whom the catheter can pass the stenosis The catheter may be pushed into the aorta and pressure in the aorta and pulmonary artery may be identical In some cases the localization and the degree of pulmonary stenosis cannot be determined with angiocardiography and catheterization The oxygen saturation of the blood in the right ventricle is identical with or even higher than that of the right atrium

Differential Diagnosis This is simple if the patient is over 3 years old for most patients with other severe cyanotic congenital abnormalities have died by this time Some forms of truncus arteriosus and pseudotruncus cannot be separated earlier The differentiation from the Eisenmenger syndrome is difficult since those cases of Fallot's syndrome with a slight pulmonary stenosis have very similar findings A complete transposition of the vessels will also have to be considered Pulmonary stenosis with atrial septal defect and patent ductus arteriosus with right to left shunt cause similar syndromes

Prognosis Surgery Most patients succumb early to the lesion although one man was known to reach the age of 59 years and a woman 64 years (Marquis) The impact of surgery on the duration of life cannot be estimated at present In the absence of dyspnea and squatting surgery is not justified There is no doubt that in patients with marked cyanosis dyspnea and convulsions marked improvement follows surgery The convulsions seem to be caused by a sudden marked right to left shunt and are treated by the administration of oxygen and Demerol

Three types of operation are in use First there is the Blalock Taussig operation now classical in which an arteriovenous fistula is created The pulmonary ischemia is improved by the creation of an anastomosis between the subclavian or the innominate artery and the pulmonary artery The operation is performed when there is evidence that a significant pulmonary circulation directly from the right ventricle is absent A pulmonary artery and systemic arteries as well must be present for the anastomosis The necessary pressure gradient must prevail in the arteries The mortality from this operation was at first about 18 per cent but soon fell to about 3 per cent in spite of great temporary improvement in individual survivors it should be kept in mind that one creates a large ductus arteriosus which strains the circulation and the heart A second operation was introduced by Potts and his collaborators in which the aorta is anastomosed side to side with the pulmonary artery Brock s procedure represents a third operation In this the pulmonary stenosis is attacked from the right ventricle This procedure is discussed in the section on pulmonary stenosis and should be the preferred method whenever feasible Surgery is preferably done when the patient is between the ages of 2 and 15

A follow up study by Potts et al of 100 children six to eight years after operation showed good results in 68 per cent and fair ones in 16 per cent Direct vision intracardiac surgery employing controlled crossed circulation has been used (Lillehei et al)

TRICUSPID ATRESIA

In this lesion a stenosis or atresia of the tricuspid orifice exists Blood reaches the left heart via a large atrial septal defect Blood reaches the lungs also with the aid of the bronchial arteries or a patent ductus arteriosus The right ventricle is very small and often is only rudimentary Pulmonary atresia or a ventricular septal defect may also be present

Patients with this lesion show a progressive general cyanosis from birth on Sometimes a peculiar unexplained paroxysmal dyspnea appears The heart is larger and a noncharacteristic systolic murmur is audible to the left of the sternum at the base of the heart A murmur may be missing Because of the larger left ventricle the apex beat may be heaving there is no pulmonary conus and the lungs are oligemic

In the electrocardiogram the P waves are large and there is a fairly characteristic left axis deviation in about 90 per cent of the patients This finding in cyanotic patients with a congenital heart lesion should arouse suspicion of the presence of a tricuspid atresia Rarely there is no axis deviation

Catheterization of the heart reveals that the blood pressure in the right atrium is high and that the oxygen content of the atrium is higher than that of the venae cavae because of the presence of an atrial septal defect The over all shunt of course is from right to left Angiocardiography shows small pulmonary arteries which are reached by the dye after opacification of the aorta The catheter

may be inserted into the left atrium and ventricle because of the septal defect

The success of the Blalock Taussig operation depends upon the size of the atrial septal defect

Ebstein's Disease

This congenital abnormality involves changes of the tricuspid valve While the anterior leaflet is often normally attached the rest of the leaflets particularly the posterior one is displaced downward toward the right ventricle The leaflets are usually fused to form a membranous structure which extends down into the right ventricle like a basket Parts of the leaflets are fused with the septum or the free wall of the ventricle Thus part of the ventricle is included into the right atrium and the actual right ventricle is small The ventricular portion proximal to the valves is very thin An atrial septal defect is usually present Often the leaflets do not arise from the annulus fibrosus but originate deeper Signs and symptoms depend to a large degree on the size of the atrial septal defect which is always present

Both dyspnea on exertion and palpitation appear early

These patients show cyanosis occasionally even at birth The heart is enlarged and clubbing is present However cyanosis may appear late and the circulation need not be changed much with mild deformities The pulmonary markings are often decreased Systolic apical murmurs and gallop rhythm over the apical area as well as arrhythmias are common The P R interval may be prolonged Paroxysmal tachycardia may occur (Brown et al) Tall P waves may also be observed Right bundle branch block is common

Roentgenography shows rather characteristic findings The right atrium is very large the aorta is narrow and the lungs are oligemic

Catheterization shows equal pressure in both atria and the catheter may be placed in the left atrium With the catheter in the right ventricle severe arrhythmias occur often

Angiocardiography shows a small right ventricle and a very large right atrium which empties slowly This examination is rarely necessary

Differential diagnosis should consider pulmonary stenosis with atrial right to left shunt atrial septal defect patent foramen ovale tricuspid atresia and Fallot's tetralogy

Ebstein's disease is not amenable to surgery One patient with Ebstein's anomaly reached the age of 79 (Adams and Hudson)

Congenital Aortic Stenosis

The occasional discovery of an atresia or stenosis of the aortic valves involving the conus the valvular area or the supravalvular part of the aorta was mentioned in the chapter on aortic stenosis This lesion is often combined with other congenital defects such as atresia of the mitral valve patent septa or patent ductus arteriosus

These rare abnormalities are caused by an abnormal development of the bulbus cordis.

One should consider the possibility of this lesion when a rough systolic murmur is heard over the right second intercostal space in an infant. This murmur may be transmitted to the cardiac apex. The second aortic sound is often normal.

PATENT *DUCTUS ARTERIOSUS*

The ductus arteriosus (often named after Botallus although he was not the first to describe it) plays an important role in fetal circulation and usually closes functionally within a few weeks after birth. Only in some cases does an opening remain after the third month of postfetal life. Asphyxia seems to retard early closure (Kjellberg et al.). One is permitted to speak of a "persistent ductus arteriosus" only if this link between the aorta and pulmonary artery persists for a longer time. This lesion is much more common in females than in males. Delayed closure may take place after the lapse of years.

Incidence. Among 88 cases of congenital heart disease discovered in school children the condition was found in 20, i. e. 23 per cent. It has been estimated that at one time 20,000 adults in the United States had a persistent patency of the ductus arteriosus. The incidence is said to be greater in the first born.

Pathology. The duct may be so short that there is practically only a fistula between the pulmonary artery and the aorta. In other cases the duct is rather long. It may be patent only for a bristle or wide enough to admit a thumb; in the latter case paradoxical embolism may occur. The diameter of the duct is greater at the aortic end than at the pulmonary end.

Mechanism. Owing to the high intra-aortic pressure, arterial blood is shunted into the pulmonary artery and therefore is forced to pass through the lungs for a second time. While the flow is ordinarily directed from the aorta to the pulmonary artery, it may be reversed. This happens not only in terminal stages but also when infants cry or suckle so that pressure in the lesser circuit rises; a similar situation may arise when the lesion is combined with other defects. The volume of blood shunted may vary from 4 to 19 liters per minute. In spite of the enormous increase of blood flow in the lungs, pulmonary arterial pressure may be normal. With the development of an increased peripheral resistance in the lesser circuit and an increase of pulmonary arterial pressure, a reversal of flow may occur with marked cyanosis often less pronounced in the head and right arm.

Symptoms and Signs. These depend chiefly upon the width of the communication. Patients with a patent ductus arteriosus may lead an active life without any handicap if the opening is small. Complaints may appear early (even in childhood) and the diagnosis is easier when the communication is broad. Cyanosis and polycythemia should arouse the suspicion of a complication. The growth of the patient is delayed. Fatigue, dyspnea, palpitation and chest pain occur.

The diagnosis is not always easy and — particularly in cases in early childhood — may present great difficulties.

When regurgitation is considerable it may amount to 75 per cent of the output of the left ventricle This results in a water hammer pulse capillary pulse and a low diastolic blood pressure as in aortic regurgitation

A systolic (rarely a diastolic) thrill is palpable over the pulmonary artery Cardiac size may be normal unless a large communication causes right and left ventricular dilatation The pulmonary artery is markedly dilated if prominent on the left cardiac border it causes mitralization This was known in older literature as Gerhardt s ribbon dullness The conus of the pulmonary artery is not always pronounced Often the heart is normal in size and the left atrium may be slightly enlarged

With small communications a systolic murmur is often heard in the second intercostal space to the left of the sternum (Gibson s murmur) This is the only auscultatory finding even with broad communications in children up to the fourth or fifth year of life A diastolic apical murmur may appear even in the first month of life In persistent right aortic arch a diastolic murmur is heard to the right of the sternum Later in typical cases there is a continuous systolic and diastolic murmur with systolic accentuation (machinery murmur) due to the fact that blood is shunted from the aorta into the pulmonary artery in systole as well as in diastole The second pulmonic sound is accentuated and the pulmonary vessels may show evidence of increased pressure In some cases no murmurs are audible if pressures in the aorta and pulmonary artery are equal

As in aortic insufficiency anginal pain may appear

At times the x ray picture of the heart is similar to that of a patent atrial septum or an incomplete pulmonary stenosis The lung fields showing pleonemia or oligemia respectively permit the diagnosis

The electrocardiogram is often normal since the increased burden is laid upon the right *and* left ventricles hypertrophy of both in a more or less parallel manner may prevent the appearance of an axis deviation

Catheterization Angiocardiography The best sign is passage of the catheter through the duct The oxygen saturation of the blood in the pulmonary artery is greater than in the right ventricle Angiocardiography sometimes shows a small filling defect in the pulmonary artery because of the mass of arterial blood shunted from the aorta The dye may be found for an abnormally long time in the lesser circuit The ductus itself may sometimes be observed in the left anterior oblique position A diverticulum like dilatation is sometimes seen in the aorta at the orifice of the ductus Retrograde aortography leads to an early filling of the pulmonary artery

Differential Diagnosis The distinction from an atrial and ventricular septal defect and from a venous hum in anemia must be considered

Even if all the characteristic signs seem to be present one must take care not to confuse the lesion with an aortic pulmonary septal defect a left ventricle right atrium shunt in a high interventricular septal defect or rupture of an aneurysm of the right aortic sinus into the right ventricle or arteriovenous pulmonary fistula

The diagnosis is more difficult when only a systolic murmur is present

Complications About 30 to 40 per cent of the patients used to succumb to subacute bacterial endocarditis This lesion is usually located around the duct and in the wall of the pulmonary artery where blood from the aorta strikes the vessel Approximately 15 per cent develop a pulmonary aneurysm which may rupture

Another large group of patients develops congestive heart failure Never thele s patients may reach the age of 60 without awareness of the lesion and survival to 79 years is known Congestive heart failure develops early when all signs are distinct A patent ductus may close spontaneously

The combination of patency of the ductus arteriosus with other lesions is common In some ca es of stenosis of the pulmonary valves for instance patency of the ductus arteriosus is a necessary complication to prolong or even to maintain life In patients who live beyond childhood uncomplicated ductus arteriosus is however the rule

Reversed blood flow from the pulmonary artery into the aorta due to pul monary vascular changes is a serious complication These changes (fibrous intimal proliferation) are sometimes present at birth

Surgery The diagnosis of patency of the ductus arteriosus has assumed importance since as Gross showed (1939) the duct may be successfully closed by ligation

The decision to operate on a patient with a patent ductus arteriosus is fraught with difficulty One must at first rule out the existence of other congenital lesions Complications during or immediately after the operation create a mor tality of about 5 per cent when all cases operated on are included In experienced hands the operation results in a mortality that is now less than 1 per cent Some of the earlier patients succumbed to acute infections this is prevented at pre ent by administration of penicillin Occasionally the duct is very short and for practi cal purposes an arteriovenous fistula between the aorta and pulmonary artery exists In these cases ligation is impossible but successful surgery has been done

Patients with patent ductus arteriosus should be carefully watched and the operation performed between the ages of 6 and 12 years If the patient is 35 years or older and in good condition operation is unnecessary Moreover no surgery should be undertaken in patent ductus arteriosus with a reversed flow since the high pressure in the le ser circuit often leads to acute right heart failure

The danger of operation on the other hand is opposed by the ever present possibility of the development of subacute bacterial endocarditis and decom pensation Therefore every case must be judged according to its own merits It is however clear that patients who had subacute bacterial endocarditis impending decompensation or those with marked enlargement of the right and left ventricles need operative intervention Complete cure has been reported repeatedly following the operation in cases already complicated by subacute bacterial endocarditis The operation should not be undertaken in children under the age of 6 years since delayed spontaneous closure does occur The clearer the

evidence is that a wide communication exists with marked shunting of blood (low diastolic blood pressure enlargement of the heart) the more likely a shortened life and the clearer the indication for operation

The persistence of murmurs of a patent ductus arteriosus after its ligation is an interesting problem Actually ligation does not obliterate the duct and does not prevent the formation of eddies It is probable however that in patients in whom a diastolic murmur persisted the duct has not been successfully ligated Recanalization has occurred with simple ligature in 10 per cent of the cases operated on This reason plus the added fact that a pulmonary aneurysm may be present has made division of the duct and careful suture of both ends the method of choice

Coarctation (Isthmus Stenosis) of the Aorta

Incidence This interesting anomaly a narrowing or complete occlusion of the aorta after the departure of the large arteries is not as uncommon as many believe It is said to occur in one of every 1000—1 500 necropsies

The malformation is 4 to 5 times as common in males as in females Although it is often overlooked the diagnosis is easy if a search for certain signs is made The lesion has been observed in brothers (Klemola)

Pathology Two varieties are recognized In the infantile type the stenosis involves the aortic isthmus between the origin of the left subclavian artery and the ductus arteriosus Sometimes this part of the aorta is converted into a fibrous cord The ductus arteriosus is usually patent the circulation in utero persists and there is no collateral circulation Often additional malformations coexist The lesion is serious and afflicted children die within one year

The adult type consists of a short narrowing or atresia at before or just below the insertion of the ductus arteriosus which is usually but not always closed The amount of stenosis varies considerably and milder grades are compatible with long life In one oft cited patient death occurred in the ninety second year A narrowing of the aorta in this area for 1—2 mm occurs physiologically

Since the time of Skoda the development of the lesion has been associated with the physiologic closure of the ductus due to an extension of the obliterative process of the ductus into the aorta Some facts speak against this conception Thus the ductus may be patent in some cases of coarctation of the aorta An abnormal junction or abnormal regression of the primitive branchial arteries is responsible

Not rarely there is complete occlusion (atresia) The lesion may occur far down in the thoracic aorta and even in the abdominal aorta down to the iliac arteries The aortic valves are bicuspid in 25 to 40 per cent of the cases In 10 per cent the aorta is hypoplastic If the ductus arteriosus is patent and brings venous blood into the aorta the oxygen saturation of blood in the head and upper extremities is normal but in the lower extremities it is subnormal These parts may be cyanotic

The diagnosis is more difficult when only a systolic murmur is present

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Fig 58 Notching of the ribs in a patient with coarctation of the aorta

The mechanism of the hypertension is still disputed Animal experiments suggest that this is not due to mechanical factors but to an interference with the blood supply to the kidneys which causes the release of pressor substances If this were the case an increased pressure should also be expected in the lower extremities There is some evidence that peripheral vasoconstriction is general in these cases Unknown mechanisms may also interplay The blood pressure *may remain elevated after successful therapy but any elevation of blood pressure* may persist even after removal of the cause

Coarctation of the aorta should always be suspected when high blood pressure is detected in a young individual and is not readily explained by a positive family history of hypertension

As stated earlier the absence of a femoral pulse should always make one suspicious of an aortic coarctation in an adult In children however the femoral artery may pulsate (Gruner and Herbst)

The electrocardiogram often shows left axis deviation and evidence of left ventricular hypertrophy

Roentgenography The diagnosis is usually established by characteristic x ray findings In the left anterior oblique position a defect in the aortic outline can be seen

Very important are the erosions of ribs As the result of the widening and the strong pulsations of the intercostal arteries erosions appear on the lower part of some of the ribs these can be easily demonstrated (figure 58) The erosions are absent from the first two ribs and they may be missed in the last three *They are present in about 75 per cent of patients with coarctation The scalloping* is due mainly to the tortuosity of the arteries actually it is not on the lower border of the ribs but is found at the junction between the main bodies of the ribs and the thin portion that forms the costal groove This abnormality has also been seen unilaterally in other lesions (tetralogy of Fallot) Notching of the ribs on the left side alone occurs when the right subclavian artery arises distal to the coarctation or when this artery is stenotic (Love and Holms) Right sided notching appears with coarctation of the aortic portion between the left carotid and left subclavian arteries Notching of the ribs develops after division of the subclavian artery after Blalock s operation for pulmonary stenosis (Kent) Rib notching has been seen in a baby five months old (Gruner and Herbst) but usually appears in 6 to 10 year old patients In neurofibromatosis with participation of the intercostal nerves notching of the ribs may be observed

Tomography may also show the stenotic area

The vascular shadow is often deformed The widened left subclavian artery may cause a bilobate shadow on the upper left cardiac border The upper lobe is formed by the aorta the lower lobe by the subclavian artery The aortic knob may be absent and it may appear bilobate owing to the widening of the post stenotic aorta The widened left subclavian artery may be confused *with the* aortic arch

Abnormal esophageal patterns due to kinking of the aorta because of post stenotic dilatation occur (Figley) Bruwer describes a notch in the left border of the descending aorta above the level of the pulmonary artery it occurs in one third of the patients with coarctation In lateral x ray pictures the widened mammary arteries are visible (Odmann)

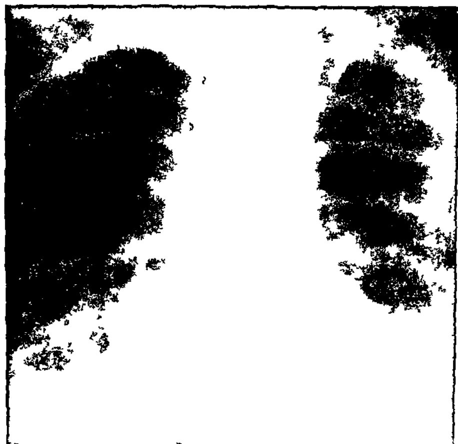


Fig 59 Retrograde aortography reveals coarctation of the aorta in a 23 year old woman

Further Comments In 24 of 40 patients with coarctation Grantstrom found corkscrew tortuosities of the retinal arteries

When coarctation develops proximal to the ductus arteriosus no adequate collateral circulation develops before birth (Bahn et al)

The lesion is often combined with other anomalies such as a bicuspid aortic valve and abnormal origin of the left subclavian artery

By virtue of the impaired blood supply the development of the lower half of the body may be somewhat retarded in contrast to the upper half thereby resulting in a body that is malproportioned The discrepancy may also be evident in the color and temperature of the two regions

Ballistocardiogram This often shows a decreased length or absence of the K wave which is caused by the impact of the ejected blood into the aorta This sign however is also found in thrombosis of the abdominal aorta (Leriche syndrome) On the other hand deep K waves have occasionally been found in patients with coarctation

Catheterization and Angiocardiography Cardiac catheterization does not contribute to the diagnosis Intravenous angiocardiography is also often of little value since the dye has been diluted too much by the time it reaches the aorta The best method is to inject the contrast medium directly into the pulmonary artery or right ventricle Retrograde aortography with local deposition of the dye has been attempted The stenosis is then visualized when the patient is in the left anterior oblique position (figure 59)

Complications Many patients die of left ventricular failure In 40 of 200 cases spontaneous rupture of the heart or aorta above the stenosis caused death The aorta may rupture directly into the pericardium or a dissecting aneurysm may form Mycotic endaortitis and cerebral hemorrhage also are common Aneurysms of the circle of Willis are not rare Consequently the patient should not perform heavy physical labor

A mitral stenosis occasionally coexists

Prognosis It has been found that 25 per cent of the patients may attain a fairly old age 25 per cent develop subacute bacterial endocarditis (aortitis) and 25 per cent have rupture of the aorta Others die from cerebral hemorrhage or decompensation It is estimated that 61 per cent die before the age of 40

Surgery Removal of the stenotic area and end to end anastomosis of the aorta was performed for the first time by Crafoord and Gross in 1944 The mortality from this operation is now less than 5 per cent The operation is not undertaken if the blood pressure is normal Moreover surgery is seldom performed in patients beyond the age of 30 years since the aorta at this age has lost much of its elasticity so that an end to end anastomosis is not feasible If the section of the aorta removed is long and the two ends cannot be reunited a graft of homologous aortic tissue is used The operation is not performed in childhood since the lumen of the operated area will not widen as the patient grows After a successful operation the blood pressure gradually falls but not always to normal levels Improvement is slow and does not follow surgery immediately At times patients 40 years of age have been improved while others only 20 years of age failed to respond to operation (Hallenbeck et al)

ABNORMALITIES OF THE AORTIC ARCH AND ITS GREAT ARTERIES

There are a large number of variations of abnormalities in this area (Edwards et al) but they require no description in this book However since some of them have serious consequences when they compress the trachea and esophagus they will be briefly mentioned at this juncture

During the development of the aorta and the pulmonary artery with their branches certain arterial arches (branchial arteries gill arteries) appear and

disappear There are six arteries of this kind on each side but all are never present at the same time The aortic arch normally develops from the left fourth branchial artery while the right one undergoes obliteration If the right fourth branchial artery and the left one persist the aortic arch is double Usually however a larger part of the left arch vanishes and a persistent right aortic arch results

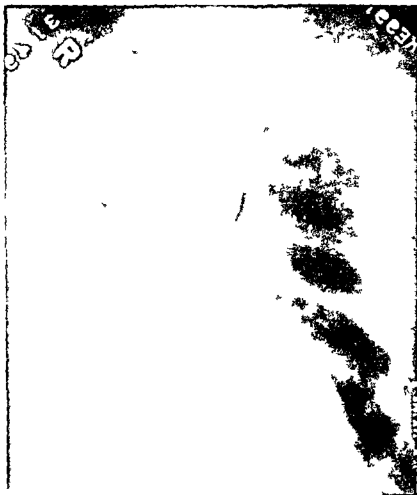


Fig 60 Abnormal esophageal pattern in a patient with persistent right aortic arch (p a picture)

This condition is not rare but since it causes no symptoms in the majority of cases discovery is accidental on occasion of an x ray examination Other anomalies such as coarctation of the aorta often coexist

Many variants are known which depend mainly on how much of the left aortic arch persists and on the site of origin of the left subclavian artery The

persistent right aortic arch rides the right main bronchus and then proceeds forward and to the left usually behind the trachea and the esophagus

The typical x ray picture consists of the absence of the usual aortic knob and its appearance on the right side or bilaterally with the descending aorta at

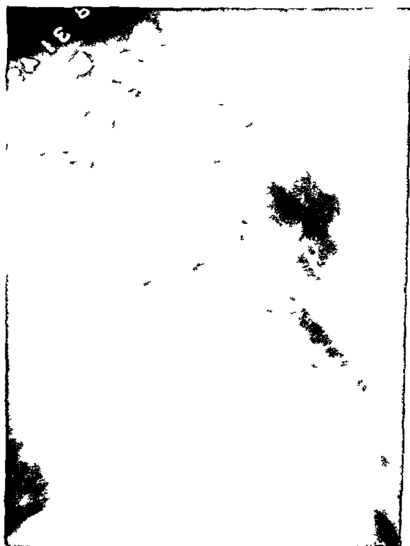


FIG 61 The esophagus is displaced forward in the right anterior oblique position (persistent right aortic arch)

the right upper cardiac border If the esophagus is filled with barium the convexity of the aortic impression in the esophagus in the postero anterior position is directed not to the right which is normal but to the left (figure 60) In the right anterior oblique view the esophagus and trachea are displaced forward by the aorta which swings behind it from right to left (figure 61) The aorta may be

widened and may form a diverticulum at this place Compression of the esophagus by the vascular rings may cause dysphagia (dysphagia lusoria) Death has resulted from compression of the trachea and esophagus In some cases the ductus arteriosus originates on the right side from the aorta and travels behind the esophagus and trachea to the pulmonary artery on the left side The aortic rings may be patent or fibrotic

Dysphagia may also be a symptom if the right subclavian artery arises at a point distal to the origin of the left subclavian artery and crosses to the right between the esophagus and the vertebral column

TRANSPOSITION OF THE GREAT ARTERIES

If the development of the bulbar part of the ventricles is disturbed and there is an abnormal torsion in this area a transposition of the pulmonary artery and aorta results This is usually combined with other abnormalities especially with ventricular septal defects Several subvarieties are recognized

The defects are interesting because they are not explained by a mere disturbance of development In ontogenesis no stage is reached in which similar conditions prevail According to the phylogenetic theory of Spitzer the lesion results from an arrested development in the early phase with the heart adapting itself to this disturbance

Type I The *riding aorta* originates from the right *and* left ventricle over a large ventricular septal defect This form has been discussed previously in connection with the Eisenmenger and Fallot syndromes Since according to Spitzer torsion of the primitive cardiac tube is one of the requirements of the formation of the interventricular septum abnormal torsion leads to a septal defect

Type II *Simple transposition* is an anomaly in which the pulmonary artery and aorta originate from the right ventricle a septal deficiency coexists

Type III In *complete transposition* the aorta arises from the right ventricle and the pulmonary artery from the left These patients must also have a large atrial or ventricular septal defect or a patent ductus arteriosus to live

The lungs are pleonemic since the pulmonary artery arises from the left ventricle The ascending aorta is situated anteriorly to the left while the pulmonary artery is posterior to the right There is pronounced cyanosis from birth The patient very rarely reaches adult life There is progressive neonatal cardiac enlargement

Type IV *Mixed transposition* is a term applied when in addition to the changes in type III the right ventricle contains only the aortic orifice while the tricuspid orifice is included in the left ventricle

In the Taussig Bing syndrome the pulmonary artery rides over both ventricles and the aorta originates in the left ventricle

In *corrected transposition* the aorta and pulmonary artery originate from the proper ventricle but their position in respect to each other is changed This aorta is situated ventrad to the pulmonary artery (see next section)

Severe cyanosis and clubbing is the rule Murmurs may be absent Deformities of the chest and kyphosis are common

Attempts have been made to improve the circulation of patients with transposition of the great vessels by surgery

DEXTROCARDIA

The heart may be located in the right chest owing to displacement by pulmonary disease effusions diaphragmatic hernia or high position of the left diaphragm (dextroposition of the heart) In true dextrocardia two main groups are differentiated

(1) *Dextrocardia with complete inversion of the viscera* (situs inversus totalis) In these patients the organs are properly located except they form the mirror image of the normal the situs solitus Other congenital anomalies are rare they may occur just as they do in other individuals Inversion of all main waves of lead I in the electrocardiogram is characteristic for this lesion The anomaly is an accidental finding without practical importance

(2) *Isolated dextrocardia with normal or partly abnormal position of the abdominal viscera* Usually other congenital abnormalities and variations are present In some variants the position of the heart chambers is normal but the axis of the heart is changed from left craniad to right caudad (dextroversion of the heart or dextrotorsion after Zdansky) At other times the position of the atria and great vessels seems normal but the ventricles are transposed If a complete transposition of the aorta and pulmonary artery coexists the lesion is corrected in an ideal manner (corrected transposition as mentioned in the previous section)

In all these varieties the electrocardiogram may be normal or show atypical alterations

ARTERIOVENOUS FISTULA

Systemic Circulation

Pathology Communications between the peripheral arteries and veins similar *to the abnormal connection in persistent ductus arteriosus have* been known since William Hunter described the acquired variety A number of other names have been bestowed upon the lesion the most popular being arteriovenous aneurysm in some instances the appearance has led to such descriptive terms as cirsoid cavernous racemose aneurysm and the like The communications are classified into two types congenital and acquired

The congenital variety is found in the neck or the extremities Usually there is a lateral anastomosis due to the presence of small communicating vessels but sometimes an end to end anastomosis exists between arteries and a venous plexus Often several anastomoses are present

The acquired arteriovenous fistula is found anywhere in the body where trauma creates a communication between an artery and vein

Signs The general effect is that blood is forced under arterial pressure directly into the venous system This causes changes in the vessels so that the artery may become venified and the vein arterialized If the fistula happens to be located in an extremity extreme engorgement and dilatation of the veins may be seen and ulceration of the skin may occur at times Occasionally the veins are so dilated that an operation is performed for the supposed varicose veins — with disastrous results The circumference of the affected extremity may be increased while the bones are so enlarged as the result of increased vascularity that local gigantism develops Since the resistance to the flow of blood through the fistula is less than to the flow through the capillary bed large volumes of blood may be attracted to the area with consequent dilatation of all nearby vessels as a result a local increase of skin temperature appears as a common sign of increased vascularity

A characteristic bruit and thrill are often present they are most pronounced over the fistula and are transmitted distally and proximally along the course of the affected vein Pressure on the site of the fistula as well as on the proximal section of the artery causes the murmur as well as the thrill to vanish If an intracranial fistula is present the patient as well as the examiner may hear the bruit

The development of varicose veins at an abnormal location early in life should make the examiner suspicious of the presence of an arteriovenous fistula Arteriography assists in the diagnosis

In the acquired type the artery and vein are usually penetrated by a foreign body — a bullet knife splinter of glass and so forth Usually the original hemorrhage is easily controlled however the arterial pressure produced in the vein may cause enormous edema and gangrene may necessitate early amputation of the extremity Some patients die immediately due to cerebral or myocardial anoxia Frequently the attendant shock and acute hypotension preclude the immediate appearance of a bruit and the thrill These signs become obvious with the improvement in the general condition of the patient The bruit and thrill are continuous throughout the cardiac cycle and a systolic accentuation often occurs

The other peripheral signs are the same as in aortic insufficiency and patency of the ductus arteriosus There is a water hammer pulse and a low diastolic blood pressure The systolic blood pressure may be elevated presumably owing to the increased cardiac output The size of the heart is increased for cardiac strain is augmented about one fifth to one half of the output may leak into the veins The left ventricle dilates for reasons that are not entirely clear some investigators claim it is caused by a reduction of coronary blood flow but we question this explanation It is also not entirely clear why dilatation of the heart is usually absent in the congenital type of lesion The early adaptation of the circulation to the lesion may play a role Decompensation may occur in the acquired type just as it happens in a patent ductus arteriosus

Fluoroscopy may show that compression of the fistula and the arrest of leakage diminish the size of the heart in the acquired type During compression

the heart rate diminishes 20 to 30 beats per minute and the blood pressure falls 20 to 30 mm Hg (Branham s sign)

Surgery If the patient is seen immediately after the development of the fistula suturing with restoration of the vessels may be considered When some time has elapsed delay in operation is justified since small fistulas may heal spontaneously also procrastination permits the development of some collateral circulation with less likelihood of gangrene if ligation of the main vessel is necessary However if dilatation of the heart has occurred spontaneous closure is very unlikely and operation is necessary (Holman)

Surgery offers great assistance in restoring normal conditions In some cases subacute bacterial endarteritis develops at the site of the fistula and can be cured by operative intervention Subacute bacterial endocarditis may also develop at the usual sites on the cardiac valves (see section on subacute bacterial endocarditis)

The previous discussion is applicable chiefly to the ordinary arteriovenous fistula of an extremity Naturally the situation is somewhat different when the fistula joins large vessels within the thorax or when the internal carotid artery and cavernous sinus are joined following fracture of the sphenoid

These problems belong to the domain of surgery and will not be discussed in detail here

Obviously the clinical picture is modified by the character of the tissue supplied or drained by the involved vessels Thus in arteriovenous fistula involving the internal carotid artery and cavernous sinus there is stabbing knife like retroorbital pain pulsating exophthalmus an audible bruit and a variety of visual disturbances In other lesions involving the carotid or vertebral arteries we have observed the gradual development of neurologic and psychiatric syndromes Whether or not surgery should be undertaken will depend upon the individual circumstances for ligation of a carotid artery for example may be followed by contralateral hemiplegia in a middle aged subject If the vessel can be compressed for an hour without the appearance of headache or weakness and tingling in the contralateral extremity constriction of the involved vessel by fascia lata may be considered

Lesser Circulation

Congenital arteriovenous fistula in the lesser circulation is a condition related to familial hereditary hemorrhagic telangiectasia (Rendu Osler Weber) It is also seen in several members of the same family but the skin and mucous membrane lesions are often missing Sometimes the lesion is bilateral It consists of a short dilated afferent artery and several dilated efferent veins with many distended vessels inbetween Secondary focal degenerative processes take place in the convolution of the vessels and added communications between veins and arteries appear This abnormality involves males as a rule and is usually recognized before the thirtieth year of life

Symptoms The chief symptoms are dyspnea and hemoptysis Petrosternal pain and epileptiform attacks occur in some cases There is dizziness faintness and attacks of uncon ciousness as well as epistaxis and headaches Some symp toms are due to anoxia and some depend upon the polycythemia

Signs The outstanding sign on physical examination is a murmur that is often continuous from systole to diastole with a systolic accentuation it becomes louder on deep inspiration and is often heard over the back

Roentgenography shows an abnormal shadow most often in a lower lobe It often enlarges on Mueller s experiment and diminishes in size during a valsalva experiment The heart is often normal in size

Tomography reveals the dilated efferent veins as a wormlike shadow and angiography is rarely necessary There is marked polycythemia with as many as 11 million red blood cells per cubic millimeter Often the fingers are clubbed and pulmonary osteoarthropathy may appear Oxygen saturation of the blood falls to 60 per cent

Differential Diagnosis At times it may be difficult to distinguish the lesion from polycythemia vera However the spleen is not enlarged and there is no leukocytosis

Therapy Lobectomy cures the disease Occasionally this also holds for certain acquired arteriovenous fistulae of the lung Thus we have occasionally encountered an acquired lesion following ill performed thoracentesis when the lung was entered and an artery and vein transfixed This accident may be reported with increasing frequency if the current popularity of pleural and lung needle biopsy persists

ENDOCARDIAL FIBROELASTOSIS

This anomaly is found in newborns and in infants although the lesion has been seen in patients over twenty years old The children suddenly develop dyspnea fainting and collapse cyanosis during crying and tachycardia appear The patients die suddenly often within 24 hours There is terminal cyanosis and the blood pressure is very low There are no characteristic findings on physical examination and the electrocardiogram often shows abnormal T waves and slurring as well as notching of the QRS complexes These signs however are not pathognomonic Complete heart block has been noted Most patients die before they complete their second year of life A few patients reach the age of 24 (Panke and Pottino) or older

Postmortem examination reveals a marked endocardial fibrosis which according to some prevents sufficient cardiac diastole just as happens with constricting pericarditis

A variety of factors have been suspected to be etiologic Inflammation fetal endocarditis and chronic anoxia have been held responsible The fact that siblings have suffered from this illness and the concurrence of other congenital abnormalities tends to support the theory that a malformation is responsible for this anomaly

THERAPY OF CONGENITAL HEART LESIONS

Treatment has been mentioned in connection with the various lesions. In addition to the suggestions offered regarding the aforementioned measures the following general remarks may be made. Physical strain should be avoided. Good over all hygiene may prolong life for many years in patients with congenital heart lesions. In the cyanotic group especially in patients with polycythemia repeated small phlebotomies help.

Great care must be taken to avoid infection of the teeth or tonsils. If present *such infections should be treated with antibiotics as a prophylaxis against sub*acute bacterial endocarditis. Some of these patients die of brain abscesses an additional indication for antibiotic therapy. For sudden attacks of anoxia, the knee chest position may help.

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Chapter 16

Anginal Pain and its Differential Diagnosis

NOMENCLATURE

A DISCUSSION OF ANGINA PECTORIS must be preceded by some remarks concerning nomenclature since the latter is rather confusing and needs clarification The nomenclature of diseases is closely associated with our knowledge of their etiology or mechanism In the past there has been much confusion with respect to the explanation of angina pectoris Huchard alone counted 80 theories designed to explain its cause On the other hand few other subjects in medicine have experienced equally great progress in recent years It is our impression that nomenclature has not quite kept pace with this progress Since the classical work of Heberden the term angina pectoris was and still is widely used to define a disease entity Heberden s description of certain sensations was so brilliant that little was added for a long time with the result that angina pectoris came to signify the same disease to every physician

That the basic mechanism underlying the condition probably is always the same — hypoxia of the heart muscle — has been suspected by many clinicians since Parry Potain compared angina pectoris with intermittent claudication Scientific progress in the last twenty years however has demonstrated that hypoxia of the heart muscle may be produced in a number of ways and that these variegated conditions have a different prognosis and require different management Therefore it seems advisable to use the term angina pectoris only to define a *symptom* The etiologic mechanism causing the angina pectoris should always be added

The classical anginal syndrome angina on effort for which the term angina pectoris is widely used at present in the majority of cases derives from a well defined lesion of known etiology that is an atherosclerotic or syphilitic stenosis of the coronary arteries or their orifices Therefore the term atherosclerotic or syphilitic coronary stenosis with angina pectoris' seems more appropriate to us than the unqualified angina pectoris

The term angina pectoris as a name for a disease entity need not be retained for historical reasons since Heberden s clinical description also includes attacks which at present would undoubtedly be attributed to coronary occlusion In describing the pain he states and I have met with one in whom it continued for several days and If it comes on in the night it will last for an hour or two These patients obviously did not have a simple angina pectoris

In recent years the term coronary insufficiency has found wide usage This term is intended by some to designate a situation somewhat between angina on effort and coronary occlusion The myocardial ischemia is more prolonged than in angina on effort and therefore may lead to slight anatomic changes Others understand coronary insufficiency to mean a chronic status of diminished blood supply to the heart muscle Still again others proposed different definitions We regard the term as a rather unfortunate designation as will be pointed out To begin with the name is incorrect because it is the coronary blood flow and not the coronary artery which is insufficient In patients with anemia or carbon monoxide intoxication the flow of blood is not abnormal but all signs of coronary insufficiency are present It is true that the phrase aortic insufficiency is employed in a similar way when an insufficiency of the aortic *valve* is meant this usage is excusable when everyone uses this term to define the same condition Apparently this is not the case in coronary insufficiency or coronary failure for these designations are applied when the heart muscle obtains insufficient amounts of oxygen because of carbon monoxide poisoning anemia pulmonary embolism or paroxysmal tachycardia It cannot be assumed that the same coronary insufficiency is operating in all these conditions Coronary insufficiency is not a diagnosis

We shall see that many instances of so called coronary insufficiency actually concern small myocardial infarctions due to occlusion of small vessels this will be discussed in a later section In some instances infarctions occur because of a combination of a mere coronary stenosis with overexertion or tachycardia

We consider the term coronary insufficiency permissible only if it is used to define a pathophysiologic state and is further qualified e g coronary insufficiency due to acute hemorrhage coronary stenosis caused by a syphilitic aortitis and so forth It is not a term to indicate a certain illness

In the following chapters the term angina pectoris or anginal pain will be used to define a pain caused by hypoxia of the heart muscle The various conditions in which this type of pain may occur will be described In an endeavor to apply in this field of cardiology a nomenclature based on etiology — a procedure so successfully promoted by the New York Heart Association for other cardiovascular diseases — we will discuss angina pectoris as a symptom occurring in a variety of conditions The term will not be used to describe a disease entity The phrase coronary insufficiency as a diagnosis is not used at all

ANATOMY AND PHYSIOLOGY OF THE CORONARY CIRCULATION

ANATOMY OF THE CORONARY ARTERIES

The right coronary artery originating in the right sinus of Valsalva runs in the atrioventricular sulcus to the posterior aspect of the heart and forms the descending posterior branch in the posterior interventricular sulcus It supplies two thirds of the *posterior aspect* of the right ventricle but it does not nourish

the area of the right ventricle near the anterior interventricular sulcus Furthermore it supplies the right margin of the heart and the inferior or basal portion of the left ventricle posteriorly It is also responsible for supplying the right atrium and the posterior third of the interventricular septum Important branches are sent to the sinus node the atrioventricular node the bundle of His and the bundle branches

The left coronary artery is usually wider than the right It originates in the left sinus of Valsalva and divides into two main branches One branch the left circumflex artery supplies the left margin of the left ventricle and most of the left atrium The descending branch of the left coronary artery runs in the anterior interventricular sulcus and supplies the anterior part of the left ventricle as well as adjoining parts of the right ventricle It also nourishes the anterior two thirds of the interventricular septum Approximately 40 per cent of people have a branch of the left coronary artery which supplies the sinus node

While this description of the blood supply holds for nearly 90 per cent of normal subjects exceptions and variations occur in 10 per cent They are most *common in the circumflex branch of the left main coronary trunk This vessel* occasionally supplies larger parts of the basal and posterior aspects of the left ventricle

Thickening of the intima of the coronary arteries is a sign of aging In childhood the intima is already as thick as the media and in the aged the intima is several times as thick as the media

Congenital abnormalities of the coronary arteries such as a single coronary artery for the whole heart more than two coronary orifices and origin of a coronary artery from a pulmonary artery are frequently observed

The left more rarely than the right (or both) coronary arteries can arise from the pulmonary artery (Soloff) This may be compatible with life up to 60 years when sufficient anastomoses between the two coronary arteries exist but it often is associated with sudden death early in childhood The children show pallor perspiration cyanosis or dyspnea The heart is enlarged and gallop rhythm is often present The T wave in the electrocardiogram is deeply inverted in lead I and sometimes also in lead II The T waves in the chest leads are also inverted but this is often seen under normal conditions in children

A single coronary artery is usually compatible with a normal function but it creates a dangerous situation when coronary occlusion occurs

Absence of coronary orifices has been seen in a child 14 months old (Grant) where the necropsy revealed blood filled spaces which communicated with the lumen of the ventricles and the coronary vessels

An interesting instance of an anomalous left coronary artery which communicated directly with the right ventricle and caused a machinery murmur of a patent ductus arteriosus has been reported (Davis et al)

Congenital or mycotic aneurysms of the coronary arteries occur and are often multiple

Complete obstruction of the coronary sinus vein does not seem to exert an adverse influence on cardiac activity (Grant)

Anastomoses

Anastomoses between the branches of the two coronary arteries are numerous Normally they are too small to function satisfactorily if one of the communicating vessels is suddenly occluded The coronary arteries are therefore called functional end arteries Hypoxemia anemia and the use of nitrites enhance (in the experimental animal) the widening of anastomoses The normal physiologic anastomoses are not wider than 40 micra The anastomoses are said to increase with advancing age but this fact is denied by others Anastomoses widen with a slowly progressive stenosis of one of the branches

Thebesian Vessels The existence of thebesian veins has often been denied but careful studies have confirmed their existence and provided detailed knowledge of the anatomy The coronary arteries communicate with the thebesian vessels only through the capillaries The thebesian vessels are particularly numerous in the right ventricle This circumstance together with the more abundant anastomoses between the coronary arteries within the right ventricle contribute to prevent damage in this ventricle in coronary artery diseases Even if a complete occlusion of a coronary artery supplying the right ventricle occurs it is rarely accompanied by infarction in the right ventricle

Arterioluminal and Arteriosinusoid Vessels Important communications between the coronary arteries and the ventricular cavities are provided by the arterioluminal and arteriosinusoid vessels The former were noted by Vieussens they originate from the arterioles and have a diameter up to 1 mm They are not abundant but provide a short circuit from the arteries direct to the ventricles The arteriosinusoid vessels also begin in the arterioles but they break into wide tubes of irregular shape they are very numerous and have a capillary like structure Not much information has been obtained concerning the function of these communications under normal or abnormal conditions

Extracardiac Anastomoses The coronary arteries also communicate with extracardiac arteries Most numerous are the anastomoses between the coronary arteries and the vasa vasorum of the aorta and the pulmonary artery The first portion of the ascending aorta is nourished by vasa vasorum originating from the coronary arteries particularly from the right coronary artery These extracardiac vessels may attain remarkable size and they certainly play a great role in nourishing the heart when the main branches of the coronary arteries undergo slow occlusion Furthermore the coronary arteries communicate with the pericardial diaphragmatic pulmonary and esophageal arteries

It is possible for aortitis to occlude both coronary orifices completely without impairing cardiac function and without the development of myocardial infarction This speaks in favor of the functional capacity of the cardiac and extracardiac anastomoses

CARDIAC NERVES

Adrenergic sympathetic fibers are found throughout the myocardium There is however no anatomic or experimental proof that inhibitory vagal effects exist in the mammalian ventricles with the exception of the vasoconstrictor fibers of the coronary arteries Vagal fibers are found in the atria of all animals and in the ventricular muscle of many lower animals but have apparently disappeared in the course of evolution in the ventricle of mammals A teleologic explanation of this fact is obvious Animals with inhibitory vagal fibers in the ventricle did not long survive the stresses of life

CORONARY BLOOD FLOW

Blood Pressure On the basis of experiments with denervated heart lung preparations it was long believed that coronary blood flow depended exclusively on mean aortic pressure Investigations on hearts with intact nerves and improved technique however have shown that this is not the case A priori sole dependence of coronary blood flow from aortic pressure was unexplainable for it was known that coronary blood flow can increase multifold on exertion whereas the blood pressure increases only slightly

The heart behaves like other organs of the body in regard to its arterial blood flow It takes the quantity of blood needed from the aorta and does this within limits quite independently of the blood pressure It is not passively perfused Under normal conditions about 5 to 10 per cent of the cardiac output is taken by the coronary arteries and this amount increases decidedly during exertion Widening of the coronary arteries is accomplished mainly by reflexes and partly by the action of local metabolites

Autonomic Nerves The denervated heart always shows a maximal coronary blood flow Therefore continuous nerve tonus may be assumed to control the width of the coronary vessels in the heart in situ and to permit changes in accordance with momentary needs At present there is wide agreement that the vasoconstrictors for the coronary arteries arise in the parasympathetic system and that the adrenergic vasodilators are provided by the sympathetic system While some investigators conclude from their experiments that an increase or decrease of the tonic vagal innervation is chiefly responsible for alteration of coronary blood flow others believe that the vasodilating sympathetic nerves which emerge from the eighth cervical and first to sixth dorsal segments and are carried over the stellate ganglion represent the major factor The problem of the innervation of the coronary arteries is not yet fully solved

In addition to the aortic pressure and the tonus of the autonomic nerves (at times also the secretion of epinephrine by the adrenals) the coronary circulation is changed by (1) reflexes from various parts of the body and (2) by contraction of the myocardium in every phase of the cardiac cycle

REFLEXES Reflex changes of coronary blood flow play a very great role in coronary pathology but experimental data on this subject are scarce The

reason for this as pointed out before lies in the difficulty of demonstrating autonomic reflexes in experimental work To a high degree the different reflexes depend on the status of the receptors the nerve centers and the effector organs and these factors are altered through anesthesia Sufficient facts are known however to estimate the great part these reflexes play under certain circumstances

It is a common clinical observation that an attack of angina pectoris is experienced more often or exclusively after a heavy meal This occurrence is easily explained and will be discussed in one of the following sections Occasionally however the pain develops with the first few mouthfuls of food when the patient begins to swallow quite independently of the quantity and quality of the meal This event is explained by the diminution of the coronary blood flow after mechanical distention of the lower esophagus and stomach This vago vagal reflex disappears after the vagi are severed or after atropine is administered

There are a fair number of reliable observations regarding the appearance or aggregation of objective cardiac phenomena during gall bladder disease and their disappearance after the removal of the diseased viscus (Fitz Hugh and Wolferth)

Mechanical or chemical stimulation of the nasal mucosa decreases the coronary blood flow This is due to a reflex inhibition of the sympathetic vaso dilators (Gilbert et al)

Some physicians deny the existence of narrowing of the coronary arteries by nervous and humoral influences The coronary narrowing following an acute hemorrhage which will be discussed later and the marked narrowing following an intravenous injection of Pitressin show that this viewpoint is not justified

EFFECT OF SYSTOLE The phasic changes of blood flow during cardiac activity are a widely disputed topic Time and again it was assumed that coronary blood flow stops completely during systole while others conclude from their observations that the flow is enhanced by cardiac systole According to the studies of Wiggers and his co workers the phasic blood flow in the coronary arteries depends upon two factors (1) the pressure head in the aorta (2) the intramural tension The increased intramural pressure during the isometric period reduces the coronary blood flow but with the rise of systolic pressure in the ejection period the flow increases again The flow decreases again in diastole when the blood pressure is low There is a gradient of pressure from the outer layers of the myocardium to the subendocardial layers The latter are exposed to the high intraventricular pressure and the arteries are compressed during systole The outer layers of the myocardium are exposed to the negative pressure within the chest Increased heart rate reduces the coronary blood flow

Adaptation to Work Performed Under normal conditions the coronary blood flow is adapted to cardiac activity The arterial blood necessary for the heart for a given amount of work may be inadequate when the activity is increased It is not the absolute quantity of the coronary blood flow but the relation between the supply and demand that has primary importance

Increased work by the heart is accomplished in two ways (1) The minute volume may increase mainly by a greater stroke volume while the rate increases but slightly the return of blood to the heart is augmented so that diastolic filling and therefore the systolic output becomes greater (2) The same goal an increased minute volume can also be accomplished by a greater heart rate without marked changes of the stroke volume

The heart like any other engine consumes fuel (nutrient substances and oxygen) The paramount question from an economic standpoint is whether the relation between work performed and fuel consumption remains within a reasonable limit Investigations concerning oxygen consumption and cardiac blood supply during increased activity show that the heart muscle needs much less additional blood (oxygen) if it does the additional work by a larger stroke volume and a slow rate rather than by a small stroke volume and a fast rate Actually the heart of athletes during the training period adapts itself to a low rate and a larger stroke volume (Bainbridge) and therefore to the more economic type of heart action

These facts explain the clinical observation that even a slight increase of rate in certain cases of coronary disease has a detrimental effect If we possessed a remedy which could slow the heart rate and enable the heart to increase its activity only by greater filling we might obtain excellent therapeutic results in many instances of coronary disease

Epinephrine The importance of maintaining an increased blood supply when the demands are greater is well illustrated by the observation of the effect of epinephrine and atropine on the heart Epinephrine dilates the coronary arteries and increases the blood supply to the myocardium by as much as 50 per cent The increased rate the increased motility of the muscle and the higher metabolism following the administration of adrenaline however raise the oxygen requirement so much that myocardial ischemia may develop Even healthy young individuals with normal coronary circulation may experience anginal pain after the administration of only 1 ml of a 1 1000 solution (Paab) When the existence of coronary disease is suspected in a patient the administration of epinephrine in any amount is forbidden

Atropine Atropine also acts as a dilator of the coronary arteries by inhibiting the tonic vasoconstrictive action of the vagus It has been found that atropine more than amyl nitrite increases coronary blood flow (Rein) Atropine however usually increases the heart rate as well This leads to a greater demand for oxygen Accordingly patients in whom atherosclerosis precludes a dilatation of certain coronary branches or patients with syphilitic stenosis of the coronary ostia in which an increase of blood flow into the coronary arteries is likewise impossible may develop severe attacks of angina pectoris and very pronounced though transient changes in the electrocardiogram after the administration of a therapeutic dose of atropine (Scherf and Schnabel)

It is essential to note that neither an organic disease nor a reflex narrowing of the coronary arteries is the sole cause of ischemia and anginal pain The

failure to develop a necessary dilatation of the arteries in case of increased need for blood may be equally provocative

CARDIAC PAIN

The heart muscle as well as the epicardium seem to be insensitive to painful stimuli of chemical or mechanical origin Sensory fibers exist in the adventitia of the coronary arteries and veins and proceed over the Nervi cardiaci to the ganglion stellatum on the left side more than the right after leaving the sympathetic chain they enter the spinal cord with the white rami communicantes of the first to fifth dorsal segments The upper thoracic ganglia also receive direct sensory fibers from the heart There is no proof to show that pain fibers run in the vagus Cardiac pain is a true referred pain

Ischemia of the heart *muscle* itself does not seem to cause pain But pain may be produced by ischemia of the sensory nerve fibers running in the adventitia of the coronary vessels ischemia causes metabolites to accumulate locally just as in intermittent claudication

The sensitivity of different individuals to pain especially visceral pain varies to a great extent

Experiments in which the sensitivity of the nerve fibers in the adventitia of the coronary vessels was found high do not offer enough evidence to prove that ischemia is the real and only cause of pain in coronary disease Pain came after ligation and mechanical irritation of a coronary vessel (Singer Sutton and Lueth) Furthermore the instantaneous appearance of pain in all experiments speaks against the ischemic mechanism Ischemia can cause pain only after some time elapses and not instantly The experiments merely prove the existence of pain fibers in the adventitia of the coronary vessels

ANATOMIC CHANGES DUE TO ISCHEMIA

Ischemia of the heart muscle lasting longer than a few minutes results in necrosis of myocardial fibers particularly in the subendocardial layers around the papillary muscles and trabeculae (Buechner) Necrosis in this area appears in all conditions with a diminished oxygen supply to the heart muscle These necroses were mentioned earlier as a finding in pulmonary embolism They appear in carbon monoxide poisoning in shock and in advanced anemia particularly if the animal is forced to perform heavy physical work following an acute blood loss

Similar necroses in the myocardium have been found in patients who died after prolonged epileptic attacks and who showed normal coronary arteries Presumably they are not caused by coronary spasm but are due to the inability of the patient to breathe during the convulsions and the consequent hypoxia These necroses are also seen in attacks of angina pectoris of various types even with anatomically normal arteries (aortic stenosis) and of course in cases of coronary stenosis

ELECTROCARDIOGRAPHIC CHANGES DUE TO ISCHEMIA

The electrocardiographic changes caused by a moderate hypoxia of the heart muscle consist of a depression of the RS T segment and of the T waves in leads I and II and particularly in the chest leads (V4 V6) The RS T segment in aVR is elevated The same changes appear in the electrocardiogram if the area around the papillary muscle (which suffers at first in hypoxia of the myocardium) is damaged mechanically (Boyd and Scherf) If more pronounced hypoxia exists in circumscribed areas of the myocardium the alterations in the electrocardiogram differ depending upon the site and extent of the ischemia

THE DIFFERENT CAUSES OF ANGINA PECTORIS

A disproportion between the blood supply to the heart muscle and the need for blood can occur

(1) In organic diseases of the coronary arteries Maximal ischemia appears in coronary occlusion and slighter grades in coronary diseases with stenosis

(2) In functional disturbances of the coronary arteries (spasm or failure of necessary widening in case of need) This disturbance appears in hypertensive crises in aortic valvular lesions pulmonary embolism and in acute hemorrhage

(3) In alterations of cardiac activity (increased cardiac work at the beginning of strenuous exercise paroxysmal tachycardias)

(4) Alterations of the blood (anemia carbon monoxide poisoning)

In the following sections these conditions which have one thing in common — a greater or lesser degree of myocardial anoxia — will be described in greater detail In all of these conditions pain may or may not appear

CORONARY OCCLUSION AND MYOCARDIAL INFARCTION

HISTORY

Knowledge of the great frequency of coronary occlusion is relatively old A series of excellent monographs was written on the pathologic aspect of this subject and complications such as cardiac aneurysm myomalacia and the like were elaborately discussed Some reports even showed the possibility of a clinical diagnosis of the lesion Most of these papers remained without noticeable influence on the thoughts of clinicians and sometimes even on the thinking of the very authors of the papers They continued to diagnose attacks of severe angina pectoris or status anginosus in patients who undoubtedly had a coronary occlusion Herrick however disappointed by the lack of response to his first papers continued to teach and publish on this subject Medicine is indebted to him for the fact that in the past thirty years coronary thrombosis has become one of the cardiac diseases that is diagnosed with a fair degree of accuracy

PATHOLOGY

Atherosclerosis and Thrombosis In the majority of cases coronary occlusion is due to atherosclerosis of the coronary arteries Other etiologic factors which are mentioned later represent rather rare exceptions In some cases the athero sclerotic process with atheroma formation fibrosis and lime salt deposits leads to a progressive stenosis and finally to a fibrotic occlusion of the vessels In one investigation no coronary occlusion existed in one third of the cases when the autopsy showed the existence of an infarction Only coronary sclerosis with narrowing of the lumen was found Added stress because of exertion paroxys mal tachycardia or increased output of adrenalin (Raab) may lead to an infarction in such subjects

In a greater number of cases the atherosclerotic process in the intima impedes endothelial nutrition and thrombosis of the artery occurs at this location Sometimes an atheromatous abscess opens into the lumen of the coronary artery and embolism or thrombosis develops

In a majority of cases however the occlusion is due to the rupture of giant capillaries in the wall of the atherosclerotic coronary arteries (Paterson) These giant capillaries arise in part directly from the lumen of the artery and in part from the adventitia (Wolkoff) They are numerous and due to their enor mous size and thin walls vulnerable If their wall ruptures and consequent hemorrhage occurs the intima above it may bulge into the lumen This occludes the artery Or the rupture may lead to damage of the endothelial lining so that thrombosis develops retrograde thrombosis from the ruptured capillary extending into the coronary artery from which it arises also occurs These mechanisms are certainly responsible for a vast number of occlusions in coronary thrombosis Nelson found this mechanism in 11 out of 17 instances and according to Horn et al it existed in 62 5 per cent of hearts with coronary thrombosis Snow et al frequently found recanalization in a thrombosed artery They found several infarctions following one occlusion Contrary to what others found these authors came to the conclusion that almost every coronary occlusion causes an infarction

Embolism Coronary occlusion is occasionally due to embolism Such cases *usually concern instances of acute or subacute bacterial endocarditis* during which small thrombi are detached from vegetations on the aortic or (more rarely) the mitral valves These cases are more frequent than one might suspect from reports since only a small percentage of them are published We had occasion to observe this occurrence twice in young women under twenty years of age who suffered from subacute bacterial endocarditis Sometimes emboli are due to detached mural thrombi or to fragments of atherosclerotic plaques

Following complicated fractures fat embolism of the coronary arteries is rather common and causes a variety of cardiac phenomena which are usually misinterpreted Even paradoxical embolism into the coronary arteries is known

Syphilis Syphilitic coronary occlusion involves only the orifice of the coronary arteries and is in reality an extension of the aortitis rather than an intrinsic disease of the coronary vessels Cases of myocardial infarction due to a syphilitic stenosis of the ostia have been described but usually the process evolves slowly and therefore causes a different clinical syndrome which will be described later

Other Lesions Coronary disease in periarteritis nodosa and in thrombo angiitis obliterans is a rarity However these lesions as well as dissecting aneurysm may lead to an acute occlusion of a coronary artery and myocardial infarction Involvement of the coronary arteries in Takayashu s disease has been reported Myocardial infarction due to calcification of the coronary arteries in an infant (Traisman et al) and myocardial infarction due to serum sickness (Roussak) or sickling disease have been described

The coronary arteries may be invaded and occluded by primary or secondary neoplasms Examples of such metastases have been reported from many organs

Myocardial infarction has been observed following blunt trauma to the chest electric shock and barbiturate poisoning (Holzmann)

The atherosclerotic process occurs with equal frequency in all three branches of the coronary tree (right and left descending branches and the circumflex branch of the left coronary artery) This point must be stressed because for many years the descending branch of the left coronary artery was claimed to be the site of predilection

There are certain sites of predilection for occlusion within a branch such as the descending branch of the left coronary artery 1 cm after its origin

It is interesting that in cases examined pathologically usually at least two coronary artery branches show occlusion In many instances a new thrombosis developed in a patient who had an old occlusion of a vessel supplying the same area Sometimes occlusion occurs in all three large branches (Koch and Kong)

Necrosis of the myocardium (myocardial infarction) does not necessarily follow occlusion of a main artery This is especially true when the stenosis of a coronary artery progresses slowly and allows ample time for the collateral circu lation to develop In these cases it may be possible to fill the whole coronary arterial tree by injection of contrast medium into only one artery The width of the anastomosing vessels may increase fivefold in such instances (Blumgart et al) Gradual occlusion of the coronary arteries in dogs also permits the devel opment of a collateral circulation the latter is adequate to prevent the appear ance of myocardial damage when this artery is completely closed

The activity of collateral vessels may reduce the infarction to an area much smaller than that supplied by the occluded vessel The infarction may be situated at some distance from the site of the occlusion In one instance myocardial infarction developed with all coronary arteries patent There was a marked fibrosis of the media which apparently led to a disturbance of function but the lumina of the coronary arteries were normal in width (Feyrter)

Healing A myocardial infarction heals gradually A reactive inflammation begins at its borders Connective tissue replaces the necrotic myocardial fibers and gradually a scar forms This process is completed slowly and requires some months The necrosis is fully developed after 4 to 6 days and fibrotic tissue appears in increasing amounts in the second week but the formation of collagen sometimes takes up to three months The scar becomes denser after three or more months Small infarctions heal after 5 weeks and larger ones after 2 to 4 months The size of the infarction its location the status of the coronary vascular tree and other factors may influence the speed of scar formation

Complications which may endanger the life of the patient will be discussed in the following pages

INCIDENCE AGE SEX

Incidence The incidence of coronary thrombosis in the general population is difficult to ascertain In many cases the diagnosis is not made in many attacks a physician is not called The disease is said to cause the death of 200 000 individuals yearly in the United States In a series of 1000 consecutive necropsies of all ages and both sexes myocardial infarction was found in 4 9 per cent For unknown reasons the incidence of the disease seems to be on the increase In recent years a seven fold increase of the number of cases has been reported (Morris) This is denied by others The disease is said to be rarer in the lower income groups The incidence of attacks has been found to be greater during the summer months The familial tendency is marked (40 per cent) (Bean) This is due in part to the frequent occurrence of hypertension in the same family

Blumgart found complete occlusion or marked narrowing of at least one and often of more coronary artery branches in 40 per cent of men over 40 years of age who died from a noncardiac disease

Age Since atherosclerosis of the coronary arteries occurs even in the newborn coronary occlusion with myocardial infarction may occur at any age Coronary thrombosis caused by acute rheumatic arteritis with myocarditis and endocarditis has been observed in an infant five months old In a 13 year old girl coronary occlusion with infarction led to the development of a cardiac aneurysm and rupture of the heart (Benda) Coronary thrombosis has also been observed in young men of 18 and 22 years respectively We observed myocardial infarction in a 21 year old girl This event is not remarkably uncommon in diabetics under 20 years of age

Sex Occlusion of a coronary artery is much more common in men than women the ratio being about 8 to 1 for younger individuals In old age as well as in hypertension and diabetes the incidence of coronary thrombosis is increased in women

OTHER FACTORS

Tobacco There is no proof that moderate smoking causes coronary sclerosis and thrombosis but the incidence seems to be greater in heavy smokers

Diabetes It was noted in a previous chapter that coronary sclerosis is typical of diabetes the same holds true for coronary thrombosis In diabetes coronary thrombosis appears not only more often but usually at an earlier age Among 274 cases in one series diabetes was found in 10 2 per cent (Conner and Holt) In another series of 300 cases diabetes was present in 17 4 per cent (Bean)

In individuals suffering from diabetes for only 5 years the incidence of coronary sclerosis seems to be increased It is believed by some that coronary sclerosis is not a complication of diabetes but an associated sign which appears even in carefully treated patients who scrupulously obey instructions concerning diet (Dolger) Others believe that full cooperation of the patient with regard to diet and insulin may diminish the incidence of vascular complications (Joslin)

Hypertension In hypertensives coronary sclerosis and coronary thrombosis occur much more often than in the general population Statistics dealing with the frequency of hypertension in patients with coronary thrombosis vary but estimates suggest that it is present in more than 50 per cent of the cases

Obesity Some authors deny that the incidence is greater in the obese (Yater et al) but the majority of investigators found obese patients in greater danger of developing the disease

Occupation Coronary thrombosis was found more often in people with sedentary occupations and it has been claimed to occur more frequently in physicians This has not been confirmed Actually Welsh miners were found to exhibit signs of coronary sclerosis in the same percentage as the general population

PRECIPITATING MECHANISM

In a majority of cases coronary thrombosis occurs without any apparent cause Attacks develop at rest often at night or during the customary daily work The occurrence of a thrombosis following trauma to the chest has been widely discussed and seems established The outstanding part played by the rupture of the giant capillaries in the atherosclerotic intima in the development of coronary occlusion makes trauma and sudden strain possible factors This question has extreme importance in legal medicine Occasionally coronary thrombosis occurs during surgical shock or postoperatively caused by the fall of blood pressure (Wasserman et al) A fatty meal shortens the clotting time and may therefore precipitate an attack

Myocardial infarction has been reported following poisoning with carbon monoxide Vigorous effort in a patient with coronary sclerosis can provoke an attack Fifty per cent of the fatal attacks in soldiers of the U S Army appeared during physical exertion In such cases as pointed out above thrombosis is often absent but the combination of coronary stenosis and effort caused the attack of myocardial infarction Fifty nine per cent of the hearts of these soldiers exhibited old myocardial scars

SYMPTOMS

Coronary occlusion and myocardial infarction are occasionally asymptomatic and are discovered accidentally In many cases there are however ample symptoms and signs to permit the diagnosis

Pain This is an outstanding symptom although figures about its incidence in myocardial infarction vary While previously believed to be the rule more recent observations show that pain is absent in 30 to 40 per cent of acute coronary occlusions (Boyd and Werblow) It has been mentioned that pathologists find at least one coronary artery occluded in the heart of patients who die with a simple angina on effort Not only a fresh occlusion but also an old one of another artery is discovered in those who die after they developed the syndrome of an acute myocardial infarction for the first time Slow fibrotic occlusion is more often less painful than acute thrombosis In some subjects this acute pain is absent but coronary occlusion is followed by angina on effort In other instances pain is intermittent The beginning of an infarction may antedate the onset of acute symptoms by days In psychotic patients 82 5 per cent of myocardial infarctions were painless that is patients did not complain of pain

The pain may be so severe as to develop into the most excruciating agony In most instances the pain — which may be viselike choking or burning — appears abruptly and in its full intensity There is no waxing and waning While temporary diminution and return to its original intensity occurs usually the pain is continuous It can be so savage that repeated injections of morphine may fail to relieve it Ordinarily the distress is felt behind the upper or middle section of the sternum and it may show typical radiation to the left or right arm to the neck or jaw and to the back between the shoulders Occasionally it radiates to the abdomen and it may spread to the left thigh this with other abdominal manifestations may convince the patient that he is suffering from a stomach disorder Sometimes the retrosternal pain is missing and the pain is felt only at the left elbow the ulnar side of the left (or right) arm or the left (or right) shoulder It is rare for the pain to last less than 30 minutes usually it remains for many hours and even days (status anginous) After it disappears there may be a residual soreness in the area for several days

The extreme severity of the pain may cause immediate syncope The concurrence of extreme anxiety and the severe pain often provoke great restlessness The patient is unable to sit still he moves around covers and uncovers himself alters his position or clutches at his clothing Complete immobility in an attack with severe pain is exceptional Severe sweating occurs

Between the two extremes — most severe pain and complete absence of pain — there are all transitional stages Pain may be tolerated quite well and the patient may continue work We have seen affected surgeons finish an operation despite distress Sometimes there is only pressure or soreness and the existence of pain is emphatically denied

The severity of pain allows no conclusion as to the size of the occluded vessel the extent of the infarction or the prognosis Even with the mildest distress indeed even with no discomfort a major branch of a coronary artery may be occluded As in other visceral diseases the violence of the referred pain shows great individual variation

Similar pains of equal duration of the same character and with the same radiation occur in other conditions and will be discussed later Nevertheless every pain of the type described however mild should arouse the suspicion of a coronary occlusion but such pain should never be the sole finding on which the diagnosis is based It is a serious mistake for the physician to overlook the diagnosis of a coronary occlusion merely because the prolonged pressure behind the sternum or in the epigastrium was not severe and amounted to mere discomfort But it is also a mistake to make the diagnosis simply because there was a severe pain in the left side of the chest which persisted for some time Prolongation of the pain or reappearance of it often means propagation of the thrombus and additional infarction

Dyspnea In most cases dyspnea is absent Its occasional occurrence was however described in early reports (Obrastzow and Strajesco) Even pulmonary edema is encountered Sometimes dyspnea is severe and the history of burning pain behind the sternum is elicited only by repeated questioning If sudden pulmonary edema develops in a patient without left ventricular hypertrophy and dilatation coronary occlusion should be suspected

Sometimes tachypnea is caused by apprehension or pain and may initiate the hyperventilation syndrome

If cardiac failure supervenes the types of dyspnea due to pulmonary congestion or cardiac asthma and Cheyne Stokes respiration may appear Hiccough is not rare and if prolonged represents a serious complication

Gastrointestinal Complaints Belching and even diarrhea are frequent symptoms Vomiting may be associated with nausea Frequent retching is often noted in patients who are unable to vomit The emesis is not caused by morphine alone it happens in patients who have not received this drug for the relief of pain or dyspnea It is explained by the activity of visceral reflexes originating in the heart muscle itself Severe meteorism may develop quickly this is particularly apt to occur when the blood pressure falls markedly and venous congestion appears

SIGNS

Physical examination of the heart often yields negative results

Percussion In many instances the heart is normal in size and shape This also applies to large and multiple infarctions and is somewhat astonishing in view of the extent and severity of the existing myocardial damage Absolute bed rest avoidance of heavy meals and fall of blood pressure lighten the load on the heart so that it can cope with its tasks despite almost mortal damage Under these conditions the destruction of a circumscribed area of the myocardium

could cause only a circumscribed dilatation (aneurysm) of the heart The heart is usually enlarged in patients in whom coronary occlusion complicates an existing hypertension

Auscultation This occasionally reveals loud and pure heart sounds In a majority of cases however the sounds soon are muffled, distant and indistinct The first heart sound may be very dull This phenomenon is particularly important if it develops during observation or in the hours or days following the onset of pain With progressive recovery and scar formation the sounds regain their loudness and become distinct This sequence provides a very valuable aid in checking the improvement of the cardiac status Sometimes months elapse before the heart sounds regain their original character In other cases the heart sounds are loud despite the development of large infarctions It has already been emphasized that in the presence of emphysema obesity or a markedly convex thorax distant heart sounds should not be regarded as pathologic Distant heart sounds are of importance only when normal heart sounds had been observed previously

In many patients particularly in those who develop a tachycardia the fact that both sounds are equally intense gives the impression of an embryocardia Presystolic and — more commonly — protodiastolic and summation gallop rhythm develop Systolic murmurs may appear but more often they vanish if formerly present, because of cardiac weakness

Pericarditis An inflammation of the pericardium appears if the subepicardial layers of the myocardium are damaged (pericarditis epistenocardia) While pericarditis actually develops in a fairly large number of cases it is detected clinically in less than 20 per cent Although it is usually limited to the infarcted area sometimes it spreads over the entire heart At first nothing more than a soft systolic rub is heard usually at the apex and this is often confused with a systolic murmur later the typical tripartite friction rub appears Sometimes the friction rub may be audible only for a few hours in other cases it is easily detected for several days It is often missed because myocardial contractions are weak particularly in the infarcted area The friction rub may be audible as early as six hours after clinical evidence of coronary thrombosis is found or it may appear several days later In the second group one may assume a progressive coronary thrombosis and involvement of more branches so that the infarction extends to the outer layers of the myocardium which previously had escaped

In rare cases pericardial effusion accompanies the pericarditis This is recognized clinically on percussion by the temporary appearance of absolute flatness over the precordium a flatness of the same intensity does not develop from mere cardiac dilatation

The pericarditis in general represents a desirable complication for the local inflammation speeds the healing process The local adhesions which develop as an aftermath increase the strength of the developing scar and may prevent rupture of the heart In many cases at necropsy the myocardium in the area of

pericardial adhesions is as thin as paper and is translucent In one observation a hole over 1 cm in diameter was found through a partial aneurysm covered by a pericardial adhesion (Scherf and Erlsbacher) Histologic examination of this section revealed no myocardial fibers at all In this instance a perforation of the ventricle was closed by the pericardial adhesion and life was prolonged for a time

Fever Flevation of the temperature has great diagnostic importance It is one of the more constant signs of coronary thrombosis Usually it appears after a lapse of fifteen to twenty hours but sometimes not for two to three days The height of the temperature varies In one patient it may be slight (37 2 C) in another it may reach 41°C In the absence of complications it subsides by lysis after persisting four to seven days In some cases a slight elevation exists only for a few hours but we have seen fever persist for many weeks with no demonstrable cause In some of these patients a large infarction exists with pericarditis and pneumonitis

Congestive heart failure pulmonary edema or pulmonary infarction cause sudden increase or reappearance of fever Additional extension thrombosis or late appearance of pericarditis have the same effect

The increased temperature in cases without complications is said to depend less on the reactive inflammation developing in the area surrounding the necrotic section of myocardium or on the pericarditis than in the absorption of abnormal protein products from the necrotic infarcted area Fever occurs in the absence of pericarditis and often too soon for a reactive inflammation Accordingly the elevation of temperature is equivalent to the fever developing elsewhere in connection with necrotic processes Its relatively early appearance may be explained by the fact that cardiac contractions continuously expel abnormal substances from the necrotic myocardium into the circulation There is no explanation available for the fast disappearance of the fever

Occasionally elevation of temperature is absent In one series of cases an increased temperature appeared in only 66 per cent (Baer and Frankel) In our experience the incidence is higher

Blood Pressure The fall of blood pressure constitutes one of the most important signs of myocardial infarction During the attack of pain and in the early hours after the attack begins the blood pressure is often high occasionally it is even impressively higher than it was prior to the attack (Scherf) However it soon starts to fall more or less rapidly This phenomenon represents a very valuable diagnostic sign of myocardial infarction

The rapidity and extent of the fall are variable and have great prognostic significance In some cases the drop is immediate and shock appears Shock is diagnosed by many clinicians when the blood pressure is 90 mm Hg or less and the pulse pressure is 20 mm Hg or less On the other hand one sees patients with a systolic blood pressure of 80 mm Hg and a pulse pressure of 15 mm Hg persisting for weeks without any manifestation of shock Often even in the absence of shock the fall may amount to 100 mm Hg — for example the systolic

pressure may fall from 220 to 100 mm Hg In other cases the slow decline continues for several days and may not exceed 30 mm Hg or the blood pressure may remain unchanged If levels as low as 70 or 80 mm Hg are reached the situation becomes critical for the blood supply to the vital centers may suffer In individuals with sclerotic arteries even a moderate fall of blood pressure may appreciably reduce the blood supply to such vital organs as the cerebrum or kidneys Loss of consciousness incontinence of urine and stool facial or limb paralysis or anuria may appear — without evidence of shock — and vanish if the blood pressure again rises A fall of blood pressure may be lethal *per se*

The diastolic blood pressure also falls though less than the systolic Therefore the pulse pressure may diminish significantly

The lowered blood pressure may rise within a few hours days weeks months or even years and regain its previous level Often however it remains at a decidedly lower level despite the fact that the patient feels well shows no signs of decompensation and pursues his occupation normally This observation in particular makes it difficult to explain the fall in blood pressure by myocardial damage alone The fall is usually not due to shock for in a majority of cases it is found without severe pain or shock Experimentally a fall of blood pressure appears quickly after ligation of the descending anterior coronary artery but the resulting localized myocardial damage is soon compensated by an increased diastolic size of the heart and the blood pressure regains its normal value Occasionally there is even some overcompensation and a rise of pressure There is some experimental evidence for a reflex fall of blood pressure following myocardial damage the vagus representing the afferent path (Bezold Jarisch reflex) Further work on this important problem is needed

The marked decline of blood pressure may be accompanied by a desirable lassitude and sleepiness which make it easier to keep the patient quiet Another advantage of the lowered blood pressure provided it remains within certain limits is the reduction of strain on the severely damaged myocardium Undoubtedly many patients would not survive a large cardiac infarction were it not for the reduction of blood pressure

Urine Not uncommonly the examination of the urine discloses a slight albuminuria and glycosuria (Levine) In 100 cases investigated personally glycosuria appeared in 10 per cent The amount of urinary sugar may reach 1 per cent and acetonuria is often present The glycosuria is accompanied by hyperglycemia (Scherf) and the fasting blood sugar may exceed 300 mg per cent Originally explained by shock by renal damage or by a coexisting sclerosis of the pancreatic arteries it was later attributed to the activity of reflexes regulating blood pressure (Scherf) As in other stress situations the work of the adrenal cortex was found increased This is proved by the disappearance of eosinophiles from the circulating blood an increased secretion of catechols speaks for a greater function of the adrenal medulla (Raab) The 17 ketosteroids in the urine are increased There is also a distinct creatinuria The reflexes proceed over the carotid sinus and increase the output of norepinephrine whose

effect in elevating the blood pressure is generally known In addition fever hypoxia hypercapnia and drugs (morphine and caffeine) which are frequently given to these patients may increase the blood sugar level Hyperglycemia and glycosuria appear in the absence of shock or even pain

The glycosuria and hyperglycemia are transient and usually vanish within a few days In many patients all signs of a disturbed carbohydrate metabolism are absent if examinations including the sugar tolerance curve are made after a few days

If coronary occlusion occurs in a diabetic individual extremely careful observation is necessary since a previously mild diabetic may sink rapidly into coma

In impending coma occasionally severe pain appears in the upper abdomen and the differential diagnosis between diabetic coma without complication or coma in a case of coronary occlusion will be difficult

Nonprotein Nitrogen About one third of the patients with myocardial infarction have an elevation of the nonprotein nitrogen content in the blood This may be due to the anuria in patients with shock In other instances reduced kidney function associated with atherosclerosis of the renal vessels and the fall of blood pressure is the initiating factor A similar increase of the nonprotein nitrogen in the blood may appear in heart failure It is temporary if the patient recovers

Leukocytosis This occurs in most cases of coronary thrombosis It may be found shortly after the beginning of the symptoms and the count may reach 30 000 per cubic millimeter there is relative and absolute increase of the polymorphonuclear cells and a drop in eosinophiles It occurs before or during the fever and often lasts only for one or two days A second rise appears if other vascular occlusions occur in the peripheral arteries or in the lungs If the white blood cell count surpasses 25 000 the mortality is said to be about 100 per cent The eosinophiles reappear within 5 to 7 days Occasionally lymphocytopenia has been reported in acute infarction (Altschul)

Sedimentation Rate of the Red Blood Cells Coagulation Test Increased sedimentation rate has had great significance in the recognition and management of myocardial infarction ever since its frequent occurrence in these cases was realized The increase may not be detected until the fourth or sixth day after the occlusion but values exceeding 100 mm in one hour (Westergren method) are observed The importance of this finding lies in the fact that these abnormal values may persist for weeks after the infarction that is they may be present at a time when other clinical signs such as fever blood pressure changes and leukocytosis have long since disappeared

Acceleration of the sedimentation rate of the red blood cells is without doubt an extremely ambiguous phenomenon that should not be evaluated alone In many cases where the suspicion of a myocardial infarction exists however this finding without another satisfactory cause supports the diagnosis particularly if the values rise a few days after the attack

The cause of the accelerated sedimentation rate seems to be the absorption of protein products from the necrotic heart muscle As a matter of fact the sedimentation rate is increased approximately as long as the healing process in the necrotic portion of the myocardium is incomplete For this reason determinations of the sedimentation rate are extremely valuable in appraising the progress of the restorative process The increase of the rate roughly parallels the severity of the lesion In small infarctions the rate remains normal

Occasionally abnormal values are obtained even six to eight weeks after the infarction In these patients if no other cause (latent infection anemia) is present bed rest may have to be prolonged In a majority of cases normal values are obtained within four to six weeks In rare instances the sedimentation rate remains high for many months for no apparent reason In these cases one should proceed cautiously and permit the patient to be up and about if the clinical findings are satisfactory

The sero coagulation band of Weltman has been found a valuable substitute for the sedimentation rate in myocardial infarction

Transaminase Test The serum glutamic and oxalacetic acid transaminase (SGO T) test which seems to be of great value has been developed by La Due and Wroblewski This test is based on the fact that a tissue enzyme glutamic oxalacetic transaminase has its greatest concentration in the heart muscle The normal transaminase has a range of between 10 and 40 units The average peak in myocardial infarction is 164 units per ml (Ostrow et al) but much greater values are obtained This serum activity of transaminase is not increased by infections degenerative neoplastic or other states unless there is acute damage of the heart or skeletal muscle liver or kidney The authors worked out a relatively simple spectrophotometric test of the transaminase (aminopherase) False negative tests are rare Pathologic values are those over 48 units per ml If only one test is performed it is best to do it 24 hours after the beginning of the attack Otherwise it is preferable to perform one test about 6 hours after the onset of symptoms and a second test after 24 hours The transaminase blood levels are normal again five days after the attack The highest values were seen in patients with hemorrhagic pancreatitis (over 16 500 units)

Pulmonary infarcts may also cause abnormal tests Abnormal values are also observed in myositis In patients with bundle branch block where the electrocardiogram so often does not show the characteristic patterns the test often is of great value

Other enzymes (aldolase dehydrogenase malic acid dehydrogenase) are also increased in the blood (Siegel et al)

Other Findings Kroop and Shackman found the C reactive protein test positive in patients with myocardial infarction Wilhelm found changes in the electrolyte pattern Feldthusen and Lassen described a diminished serum iron (hypoferraemia) after coronary occlusion and cardiac trauma Serum zinc levels are lowered after myocardial infarction (Wacker et al)

X ray Examination This has limited value since it is necessary for the patient to remain in bed for several weeks An elevated position of the left diaphragm has been described (Borak) it appears in the early stages and may be due to the left sided pleurisy following pericarditis Abnormal excursions and absence of pulsation along the left cardiac border have been described in connection with fluoroscopy and kymography but these findings have only limited value and cannot be used for diagnosis Due to the multiplicity of cardiac

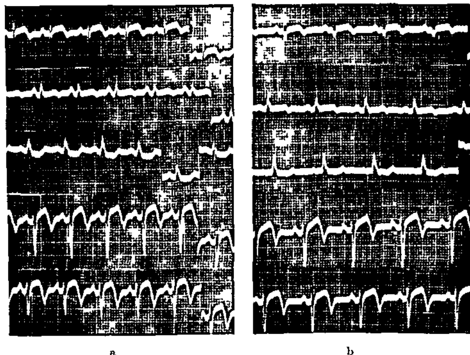


FIG 62 (a) Typical tracing of an antero lateral wall infarction obtained during the acute clinical picture in a 48 year old man There is a low QRS complex in lead I with a comparatively deep Q wave The RS T segment is elevated in lead I and depressed in lead III The R waves are low in V 5 there is a peaked deeply inverted T wave in V 2 and V 5 preceded by an elevated RS T segment Nine days later figure 62b was obtained There is a wide slurred Q in lead I followed by a deeply inverted T wave there is little change in the chest leads

movements with every systole shortening along the axis widening of some parts in the transverse diameter and rotation pulsations may be absent normally in local sections of the left cardiac border (Zdansky)

Electrocardiogram The electrocardiogram possesses primary importance in the establishment of the objective diagnosis of coronary occlusion

Experimental observations show that the alterations in the electrocardiogram may appear within 40 to 60 seconds after ligation of a coronary artery Clinically

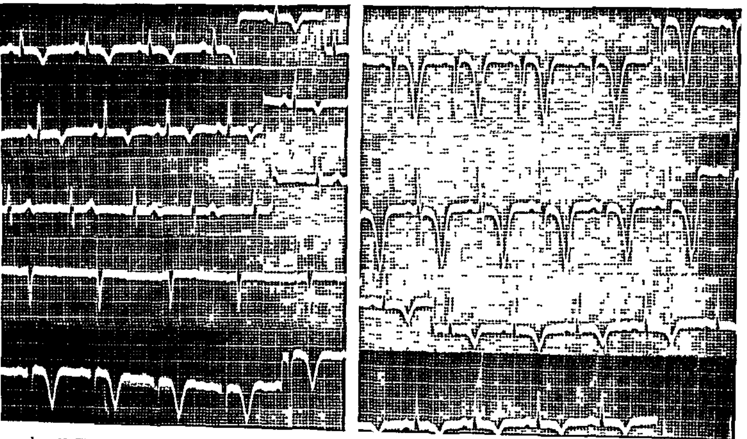


FIG 63 This figure reproduces the standard leads and the six chest leads of a 46 year old woman with an acute myocardial infarction With the exception of the absence of an R wave in V 3 there are no changes of the QRS complexes The T waves are deeply inverted peaked and symmetrical in all leads with the exception of leads III and V 1

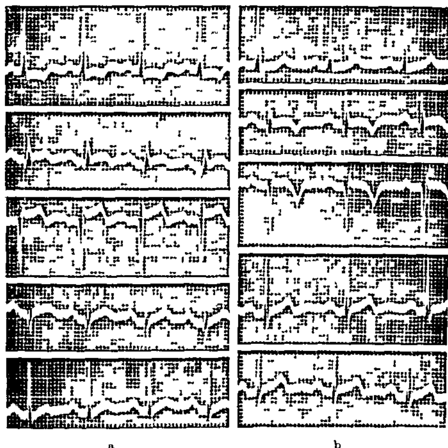


FIG 64 (a) The pattern of an inferior wall infarction 20 hours after the beginning of the attack figure 64b was obtained 22 days later

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FIGS 65—6 see pages 406 and 407

FIG 65 This electrocardiogram was obtained from a 3 year old woman suffering from an acute inferior wall myocardial infarction There is an atrial tachycardia with 2 1 block The P R interval is prolonged to 0 24 second The depression of the RS T segment in lead I and the elevation in lead III are clearly seen In V 2 V 6 there is a depression of the RS T segments which is typical for the acute stage of an inferior wall infarction

FIG 66 This is the electrocardiogram of a 56 year old man with clinical signs of an acute myocardial infarction The standard leads show only abnormal T waves there are however abnormal QRS complexes (no R waves) in lead V 2 and V 3 and a typical elevation of the RS T segment followed by an inversion of T waves in lead V 3 and V 4 The e changes speak in favor of an involvement mainly of the anterior wall of the left ventricle

FIG 67 This electrocardiogram was obtained from a 58 year old patient who experienced his second attack of myocardial infarction Lead I shows a low QRS complex with a relatively deep Q wave in leads II and III broad Q waves are present a typical elevation of the RS T segments is seen in leads V 3 V 5 An acute anterior wall infarction was superimposed on an old inferior wall infarction

Fig 65

Fig 66

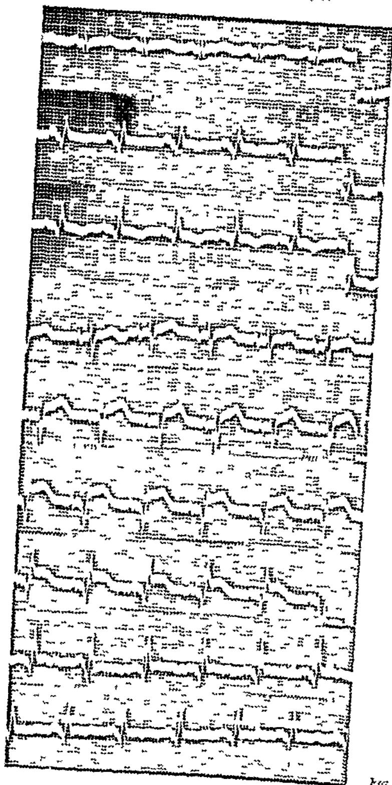


Fig 67

these alterations sometimes last for weeks or months in fact the electrocardiogram may remain abnormal throughout the patient s lifetime

In many cases the changes are characteristic and permit the localization of the infarction Certain patterns indicate an infarction of the antero lateral area or of the anterior wall of the left ventricle due to an occlusion of the descending branch of the left coronary artery other patterns indicate an infarction of the inferior or posterior part of the left ventricle due to an occlusion of the posterior descending branch of the right coronary artery

In figure 62a the typical tracing of an acute infarction of the antero lateral wall of the left ventricle near the apex is reproduced The tracing was obtained from a 48 year old man who had suffered from severe pain behind the sternum for 12 hours when the electrocardiogram was taken The tracings show the typical pattern There is a high take off of the RS T segment from the descending branch of the P wave in lead I and a low take off in lead III A very pronounced inversion of the T waves is present in the chest leads (V 2 and V 5)

Figure 62b shows the electrocardiogram of the same patient nine days later It reveals the typical evolution in the standard leads while the chest leads are almost unchanged

Figure 63 shows the electrocardiogram of a 46 year old woman who suffered from an acute infarction 12 days previously There is a deep inversion of the T waves in leads I and II as well as in most chest leads

In figure 64 a and b the typical early and late pattern of an inferior wall infarction are reproduced The tracings were obtained from a 59 year old woman The electrocardiogram of figure 64a was taken 20 hours after the beginning of pain due to myocardial infarction figure 64b was taken 22 days later

In figure 64a there is a depression of the RS T segment and an inverted T wave in lead I There is a deep Q wave and a high take off in lead III The chest leads (CR 2 and CR 4) show no changes Figure 64b shows the typical evolution with a return of lead I to normal and the deep abnormal Q waves with inverted T waves in leads II and III

Figure 65 shows the acute stage of an inferior wall infarction with 2 1 block and a prolongation of the P R interval while figure 66 shows the pattern of an infarction of the anterior wall of the left ventricle In figure 67 an acute anterior wall infarction was superimposed on an old inferior wall infarction

For a more detailed discussion of these and other patterns seen in myocardial infarction we refer the reader to our book on electrocardiography

Frequently other changes such as bundle branch block appear in the electrocardiogram but they are not characteristic Occasionally alterations are absent for days and sometimes they are missed despite many examinations Repeated tracings particularly of the six chest leads are necessary if the first records are normal

In small infarctions situated supra apically or only in the inner layers of the myocardium no changes in the QRS complex are seen and only T wave

alterations appear (figure 68a) Figure 68b was obtained 3 days later and shows a marked tendency to normalization Four days later a very pronounced inversion of the T waves is visible (figure 68c) The patient a 56 year old woman experienced pain only at admission to the hospital A propagation of the thrombus is a possible explanation for the deterioration in figure 68c However one sees in infarctions temporary normalization in the electrocardiogram (as in figure 68b) for other reasons e g an accompanying pericarditis

No conclusion is permitted with regard to the size of the infarction as is often claimed from the degree of alterations It can be shown that minute

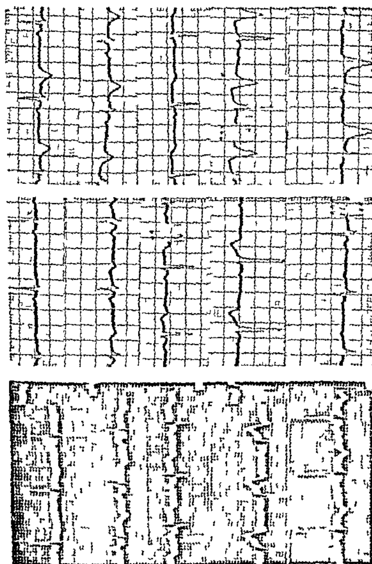


FIG 68 A 56 year old woman was admitted with clinical evidence of an acute myocardial infarction The first electrocardiogram (a) shows the changes seen in left ventricular hypertrophy and also in certain infarctions involving the inner myocardial layers The tracing obtained three days later (b) shows a tendency toward normalization (c) Changes which suggest an anterolateral wall infarction obtained 4 days after (b)

damage of the superficial layers of the myocardium in certain areas where infarctions occur typically (apex or base of the left ventricle) cause marked changes while damage of the deeper layers of the myocardium or damage of areas not in contact with the diaphragm or the long dorsal muscles in front of the spinal column cause slight or noncharacteristic alterations The extent of the alterations therefore does not give any indication about the size of the infarcted areas

Since the electrocardiogram may be markedly altered in small infarctions at special locations and may show no or only slight changes in large infarctions at other sites no conclusion as to the prognosis or the management is permitted from the electrocardiogram

In cases with bundle branch block or with old previous infarctions or even with a marked hypertrophy pattern typical changes are often missed

COMPLICATIONS

In acute myocardial infarction cardiac output falls the cardiac rate increases venous pressure often rises and the peripheral resistance increases presumably due to the output of large quantities of pressor amines as a compensatory measure

In the period immediately following coronary thrombosis certain complications may arise some endangering the life of the patient Some are partly or wholly preventable and others demand emergency treatment An awareness of these complications is indispensable

Cardiac Arrhythmias These are not uncommon after coronary occlusion and often they represent very serious complications Some observers noted them in 48 per cent of cases (Rosenbaum and Levine) Disturbances of stimulus formation are usually responsible

As early as 1881 Cohnheim reported that ligation of a coronary artery may induce cardiac arrhythmias within 30 to 40 seconds and may lead to the condition now known as ventricular fibrillation The importance of these observations for the explanation of sudden death of patients with coronary diseases was stressed by this observer

Subsequently these arrhythmias were restudied with the aid of the electrocardiogram on dogs and monkeys with the same result Following the ligation of a main branch of the coronary arterial tree extrasystoles may appear within a few minutes Sometimes hours or (rarely) even days elapse before they develop The extrasystoles are most commonly of ventricular origin but occasionally they originate in the atria Extrasystoles appear particularly after an occlusion of the right coronary artery The extrasystoles are often multiform indicating their origin from different foci attacks of ventricular paroxysmal tachycardia appear and ventricular fibrillation suddenly develops At other times ventricular fibrillation appears suddenly without preliminary extrasystoles In one series of 50 experiments on dogs ventricular fibrillation appeared in 15 animals (Harris and Hussey) In another series on monkeys ventricular fibrillation occurred in 10 of 32 experiments when the right or left descending coronary artery was

ligated The first forty minutes are the most dangerous because fatal fibrillation occurs most often during this period Ventricular fibrillation has been registered electrocardiographically during attacks in man and there is good reason for assuming that sudden death in patients with coronary disease is due to this mechanism Ventricular extrasystoles and paroxysmal ventricular tachycardias are not rare in patients with myocardial infarctions

Figure 69 shows the three standard leads of a 42 year old man admitted to the hospital because of severe chest pain Despite the presence of slurring and

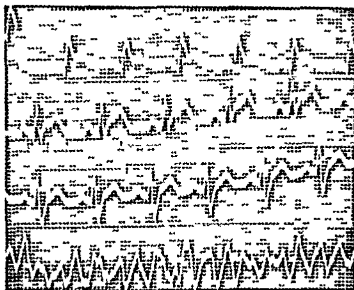


Fig 69 Acute ant ro lateral wall infarction with bundle branch block Ventricular fibrillation appeared while the el ctrocardi gram was recor led (lowermost tracing lead V 2)

widening of the QRS complexes the elevation of the RS T segment characteristic for antero lateral wall infarction is visible in leads I and II While the technician switched from lead III to lead V 2 the patient lost consciousness and ventricular fibrillation was registered

While ventricular fibrillation need not necessarily follow single extrasystoles and while experimental ventricular fibrillation may develop without preliminary extrasystoles the presence of extrasystoles shows that the patient is in danger The arrhythmias always represent a serious finding and require immediate treatment

Among 92 patients with acute myocardial infarction 20 had extrasystole and of these died (Padilla and Cossio) All four patients with multiform extrasystoles succumbed Fourteen out of 17 patients who developed frequer ventricular extrasystoles following myocardial infarction died (Woods an Barne) Other observers believe that the appearance of extrasystoles does n alter the prognosis materially It is important to realize that the sequence

extrasystoles paroxysmal tachycardia and ventricular fibrillation may appear in a few minutes and is usually not observed by the physician The authors are in complete accord with those who consider the appearance of extrasystoles after a myocardial infarction a serious complication

During asphyxia of the entire heart extrasystoles do not appear probably because there is diminished excitability of the entire myocardium

In experiments on dogs prophylactic treatment with quinidine has been found relatively ineffective In man however with the appearance of extra *systoles and to a greater extent of paroxysmal tachycardia* immediate administration of quinidine is very helpful It is claimed that the routine practice of giving daily doses of quinidine in a large hospital to all patients in danger of developing ventricular fibrillation reduced the number of sudden deaths remarkably Apart from the danger of ventricular fibrillation the damage produced in these hearts by paroxysmal tachycardia with a rapid rate per se is so great that it requires the immediate use of *quinidine* Even if large doses of quinidine are necessary the danger from it is less than that from a persistent tachycardia This question will be further discussed later in this chapter

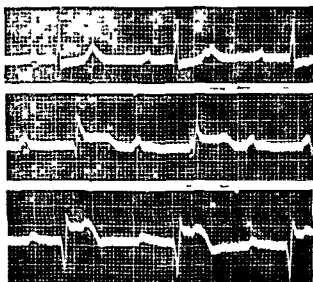


FIG 70 Complete heart block in a patient with an acute inferior wall myocardial infarction

Sometimes atrial fibrillation and flutter appear In the first condition immediate digitalization is indicated to slow the rate The latter disturbance is usually treated with quinidine but digitalis is preferred by many We often use strophanthin

It was pointed out earlier that the sinus node usually obtains its blood from the right coronary artery If the right coronary artery is occluded close to its orifice disturbances of stimulus formation in the sinus node such as sinus bradycardia or sinus arrhythmia may develop These bradycardias are beneficial because of the greater efficiency of the heart with slow rates We have seen congestive failure and gallop rhythm develop immediately after this bradycardia vanished

Since the A V node and the bundle of His are also supplied from a branch of the right coronary artery in most cases partial or even complete heart block is not rare when this artery is occluded and inferior wall infarction appears

Figure 70 shows an electrocardiogram taken from a 60 year old woman with the clinical picture of myocardial infarction There is a typical pattern of a fresh inferior wall infarction with complete atrioventricular block Atria and ventricles contract regularly but independently of each other

A partial heart block in a patient with inferior infarction is seen in figure 71 The atrioventricular rhythm in figure 72 is in all probability caused by non function of the sinus node due to the occlusion of the right coronary artery near

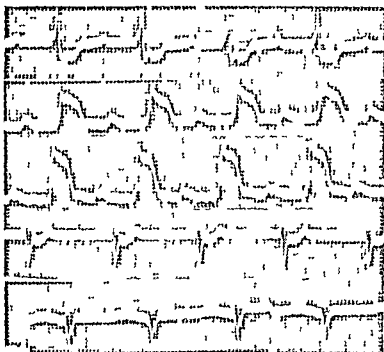


FIG 1 In a 51 year old man with the clinical signs of an acute myocardial infarction the conduction time is prolonged to 0 40 second and a block exists there is marked elevation of the RS T segment in leads II and III indicating an acute inferior wall infarction The chest leads (V 2 and V 5) show signs of an old antero lateral infarction

its orifice Auricular flutter in a patient with anterior wall infarction is seen in figure 73

All types of partial A V block and complete heart block may appear and Stokes Adams attacks may occur Sometimes the heart block vanishes in a few hours or days Under these circumstances as mentioned above the condition of the patient may change for the worse as the rate increases and sinus rhythm returns

Shock A very serious complication of coronary thrombosis with myocardial infarction is the appearance of peripheral circulatory failure or shock The cause is not clear The fall of the cardiac output or the overwhelming pain may

be responsible in some patients in other patients the appearance of arrhythmias with too rapid or too slow rates and in still other patients reflexes of the type of the Bezold-Jarisch variety may be responsible Thus central (cardiac) and peripheral mechanisms may be determining factors

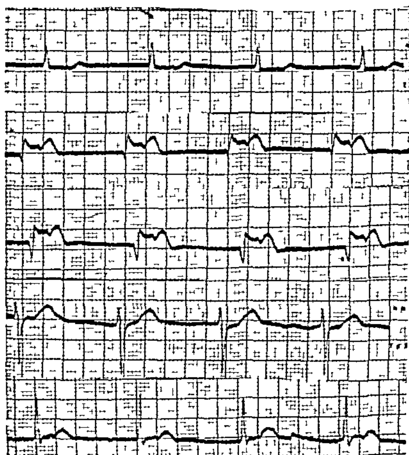


FIG 72 In a 72 year old woman with clinical signs of an acute myocardial infarction the electrocardiogram shows the pattern of an inferior wall infarction There is a bradycardia of 60 beats per minute and the sinus rhythm is replaced by an atrioventricular rhythm with a P wave (inverted in leads II and III) between the QRS and T waves

Opinions regarding its incidence vary Some believe shock occurs in 10 per cent of all myocardial infarctions while others consider it to be more rare Such diversity of opinion derives from the arbitrary method of diagnosing light shock Some physicians consider all patients to be in shock whenever the blood pressure is 90 or less while others diagnose shock whenever the pulse pressure is 20 mm Hg or less It is a good practical rule to watch the patient carefully and supervise him as constantly as one would a patient in diabetic coma as soon as the systolic blood pressure falls to values around 100 and the pulse pressure threatens to reach values around 20 In our opinion there are patients in shock

with higher blood pressure values while others have for weeks a systolic blood pressure of 80 and a pulse pressure of 20 without being in shock It is in the latter group of patients in particular that early energetic therapy may do more harm than good

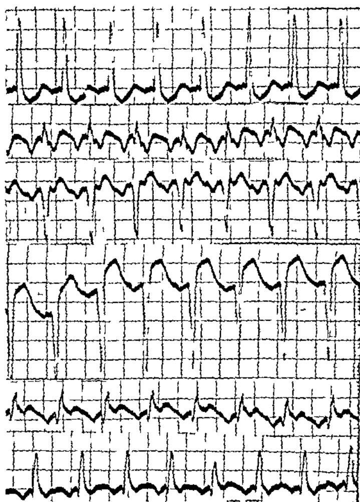


FIG 53 Atrial flutter with 2 1 block and signs of an acute anterior wall infarction (lead V 3) in a woman 78 years old

Shock should be diagnosed by other clinical signs — sinus tachycardia ashen grey color cold perspiration weakness and anuria

The mortality is markedly increased by the appearance of this complication It seems to amount to 80 to 90 per cent if severe shock is present Temporary fall of the blood and pulse pressure does occur but it is often compensated after a short time by regulatory mechanisms Even overcompensation with a rise of blood pressure may be observed (Orias) During shock the danger of

intravascular thrombosis (cardiac cerebral mesenteric) is great It may be followed by the development of lower nephron nephrosis

The early diagnosis is of importance since statistics indicate that therapy initiated when the shock has lasted more than 3 hours is of very dubious value

Perforation of the Ventricular Wall and Cardiac Tamponade Originally this event was described by Harvey Perforation of the ventricular wall in the infarcted area usually occurs in the first two weeks In one series the earliest appearance was 14 hours after the onset of symptoms and the latest was on the sixteenth day (Bean) Among 7000 autopsies spontaneous rupture of the heart was observed 40 times (0 57 per cent) (Benson et al) In another series of 25 000 necropsies cardiac rupture was seen 72 times (Edmondson and Hoxie) This tragic complication occurs in 2 to 4 per cent of myocardial infarctions Often there is no hole in the muscle but the blood oozes slowly from the infarcted area separating the layers of myocardium and cutting a tortuous path from endocardium to epicardium Rupture occurs very rarely through an old scar Many of these cases are encountered by medical examiners since the coronary occlusion preceding the cardiac rupture often remains unrecognized and the patient dies suddenly Rupture usually takes place on the anterior wall of the left ventricle above the apex The decisive factors are the amount of softening and the height of the blood pressure Rupture seems more common when hypertension persists

Rupture of the ventricular wall is usually immediately fatal Exceptions like the case mentioned above where an adherent pericardium covered the opening created by the perforation are rare

Rarely patients survive the oozing of blood and cardiac tamponade The latter is generally treated conservatively (aspiration) but surgery with suture of the involved area should be considered more often

Perforation of the Interventricular Septum This complication causes a typical clinical syndrome with the sudden appearance of a thrill and a loud systolic murmur over the fourth and fifth interspaces to the left of the sternum The heart undergoes marked dilatation and evidence of congestive failure soon appears

The patient may survive this complication for years One case was observed for four years and ten months with a perforated interventricular septum following coronary thrombosis while one of us had a similar patient under observation for three and one half years

Rupture of a papillary muscle of the left ventricle causes a loud whistling to an fro murmur that is often high pitched Sometimes there are no murmurs The clinical diagnosis is difficult Patients rarely survive more than a few hours

Postmyocardial Infarction Syndrome Dressler describes a postinfarction syndrome resembling idiopathic pericarditis Despite absence of hemorrhagic sputum in these patients we believe that the combination of pericarditis with pleurisy and pneumonitis could be explained by pulmonary infarctions Post

mortem examinations will certainly decide the issue in the future According to the author cortisone is the preferred therapy

Abscess Formation This is a rare complication in the infarcted area It appears also in sepsis pneumonia and pyelitis

Dyspnea This is a common and serious complication Often it is paroxysmal and in coronary thrombosis pulmonary edema may be the equivalent of an attack of pain Paroxysmal dyspnea and pulmonary edema may develop at any time after an infarction but they are prone to appear in the first two weeks If pulmonary congestion predominates there is continuous dyspnea and orthopnea

Moist and dry rales over the lungs for the most part at the bases are common The dyspnea is rapidly controlled by morphine which must be given day and night in these cases to afford relief Moist rales over the bases of the right and left lung are extremely common and bear continuous watching The advisability of digitalis therapy if pulmonary congestion and right heart failure supervene will be discussed later

Pulmonary Effusion Left pleural effusion is not unusual and is due to irritation of the pleura following the pericarditis A left sided pleural effusion of obscure origin in a man over forty years of age should always arouse the suspicion of a myocardial infarction Too often the infarction is overlooked and the patient is treated symptomatically for the pleural effusion

Peripheral Vein Thrombosis and Pulmonary Embolism This is a very common complication and everything possible must be done to prevent it The impairment of circulation is one of the more frequent causes of venous thrombosis all statistics dealing with the incidence of fatal pulmonary embolism stress that most of these cases concern those affected with a cardiovascular disease In patients with myocardial infarction the combination of a marked fall of blood pressure and enforced prolonged rest in bed is a typical and regular cause of thrombosis in the pelvic veins this is the usual source of pulmonary emboli Such emboli may occur as early as 10 to 15 hours after the onset of symptoms

The discussion of the effects of pulmonary emboli on the heart and circulation in a previous chapter should make it clear that this additional new burden for the severely damaged heart creates serious problems and often causes early death

The diagnosis many times is missed the symptoms or signs being attributed to a new myocardial infarction The differential diagnosis between the two conditions as well as prophylactic measures will be discussed below

Statistics about the incidence of thromboembolic phenomena in patients with myocardial infarction give figures varying from 5 to 33 per cent

Peripheral Embolism This is produced by mural thrombi from the left ventricle Since the inner layers of the myocardium are often involved in cardiac infarction endothelial damage leads to the formation of thrombi These thrombi are found in almost 50 per cent of fatal myocardial infarctions and have been noted as early as 24 hours after the onset of coronary occlusion With healing slow fibrosis occurs and only a slight thickening of the endocardium remains

Occasionally there are lime salt deposits which may be visualized by x ray In some cases on the other hand the thrombus liquifies and becomes fragmented and multiple peripheral emboli develop Despite the high incidence of mural thrombosis peripheral embolism fortunately is not very common

Embolism of the cerebral arteries causes hemiplegia and other forms of paralysis The spleen kidneys or mesentery are also frequent sites of embolism Sometimes the thrombus fragments into multiple emboli which lodge in the viscera and extremities Occlusion of a leg artery may necessitate embolectomy or amputation

Mural thrombi also occur in the right ventricle an event which usually happens when the right side of the interventricular septum is affected These thrombi may be the source of pulmonary emboli

The sudden marked fall of blood pressure in patients with severe athero sclerosis of the cerebral and peripheral vessels may lead to the formation of arterial thrombi and may cause syndromes similar to those of embolism Differential diagnosis is often impossible

If the myocardial infarction causes no symptoms the only evidence of a cardiac lesion may be one of the embolic syndromes just mentioned Embolism seems to occur often when the heart is not severely damaged by the infarction and still contracts vigorously Peripheral embolism is observed as early as 24 hours after the occlusion or as late as many weeks after

Neurologic Signs Confusion attacks of unconsciousness and epileptiform convulsions occur even in the absence of heart block or tachycardia Temporary paralysis of an extremity or the facial muscles may appear

Jaundice and Hemoptysis These are not uncommon early complications that often follow pulmonary embolism with infarction Hemoptysis occurs at times in the first 24 hours Thrombosis or embolism of a pulmonary artery or a reflex vascular spasm in the lesser circuit contribute to the development of these accidents

Cardiac Aneurysm For centuries marked dilatation of a cardiac chamber has been called an aneurysm Thus even in recent times the term has been applied to the great dilatation of the left atrium in mitral stenosis At present however the term cardiac aneurysm or partial cardiac aneurysm is reserved for a bulging of a portion of the wall of one cardiac chamber Usually the wall has undergone marked change A cardiac aneurysm may be due to trauma syphilitic gumma large tubercle trypanosomiasis (Mori et al) developmental anomalies (Martin) severe focal myocarditis (even in rheumatic fever) or a mycotic abscess but as a rule it is the result of coronary occlusion Multiple aneurysms have been described

Statements on its incidence vary Representative figures are 9 per cent (Parkinson et al) 14 per cent (Bean) and even 38 per cent (Libman) of myocardial infarctions In our experience the latter figure more closely approximates the true situation It seems that aneurysm is common in large infarctions

Early aneurysm most often develops with a massive necrosis especially if the blood pressure remains high and the patient is too active

Often the small aneurysmal sac shows a gentle rather than abrupt departure from the normal myocardium There is no sharp bulge In other cases the large sac departs abruptly and may measure as much as 10 cm in diameter Often the aneurysm is partly or completely filled with a thrombus Fortunately pericardial adhesions over the aneurysm are the rule and help to strengthen the thin myocardial wall This may be why rupture of the myocardial sac even in large aneurysms of long standing is relatively rare Most of these aneurysms follow an occlusion of the descending branch of the left coronary artery and are located slightly above the apical region of the left ventricle they occur however in the posterior basal region after an occlusion of the descending branch of the right coronary artery and in other parts such as the interventricular septum

The aneurysm itself causes no symptoms The patient usually has a history of a previous coronary occlusion with infarction although sometimes the occlusion was symptomless Because they were not kept in bed at the time of greatest softening of the myocardial wall that is in the first weeks following the myocardial infarction it is precisely these patients who develop aneurysms

In a large majority the clinical diagnosis of ventricular aneurysms is impossible by all available methods This is true particularly for those aneurysms which do not show a sharp bulge In many cases however the diagnosis is easy

The outstanding sign is an abnormal pulsation usually located slightly above the apex at the left cardiac border or slightly inside it Sometimes this pulsation on the chest wall (a bulging hemisphere) is very strong and can scarcely be suppressed In one of our cases the pulsation was seen in an area 4 or 5 cm in diameter on the sixth day after the symptoms and signs of myocardial infarction appeared Often the pulsation persists throughout the life of the patient but it may diminish in intensity or disappear with the development of thrombi or contraction of scar tissue (Scherf and Erlsbacher)

The location of this pulsation usually distinguishes it from others of cardiac origin It is too high for an apical pulsation too low for one from the pulmonary conus and too lateral for a pulsation of the right ventricle (precordial pulsation)

Dysphagia due to compression of the esophagus by an aneurysm of the left ventricle has been observed (Strandell)

Percussion usually reveals cardiac enlargement The pulse is often small and the systolic blood pressure is often very low

Auscultation often yields indefinite findings such as muffled heart sounds gallop rhythm or even pure and loud sounds Not rarely a systolic murmur is heard and is loudest over the pulsating area in some cases a high pitched diastolic murmur is audible in the same place It has the same character as a murmur of aortic insufficiency (Scherf and Brooks) (figure 78) In two patients observed by one of us the diagnosis of aortic insufficiency was made clinically postmortem examination revealed a cardiac aneurysm It is interesting to note that one of the first cases of cardiac aneurysm diagnosed antemortem presented

a diastolic murmur In this case the murmur had a musical character (Remlinger) In our experience the to and fro murmurs heard over cardiac aneurysms are soft and high pitched The murmurs must be differentiated from extra cardiac murmurs and a pericardial friction rub This is due possibly to the quality of the murmur which makes it similar to those heard in aortic insufficiency During systole the weak aneurysmal sac is filled and distended with



FIG 74 Cardiac aneurysm

blood Backflow of this blood into the left ventricle in diastole may explain the murmur

X ray examination particularly fluoroscopy is of great diagnostic help Frequently the bulge of a large aneurysmal sac reveals the diagnosis immediately Sometimes the sac is visualized only when the patient is slightly rotated Often the abdominal shadow obscures the aneurysm in these cases examination after the administration of sodium bicarbonate has been recommended since this causes a large gas bubble in the stomach with the result that much of the left lower border of the heart becomes visible Apart from the deformed contour of the left cardiac border aneurysms are sometimes recognized on fluoroscopy by abnormal pulsations like marked paradoxical outward pulsation during systole Examination in the right oblique position is often helpful One must

be careful not to confuse the fat pad on the lower cardiac border with a cardiac aneurysm

Figure 74 shows a typical aneurysm at the left border of the heart The electrocardiogram of this patient showed the pattern of an antero lateral wall infarction

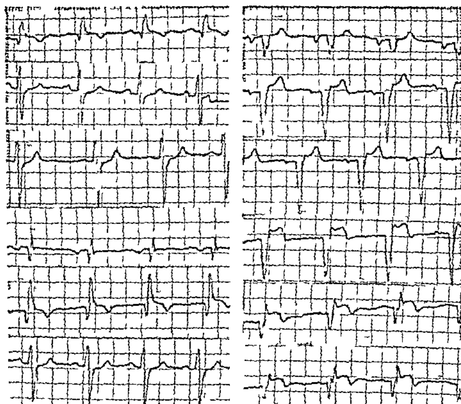


FIG 75 Typical electrocardiogram of an antero lateral wall infarction showing persistent elevation of the RS T segments in lead I aVL V3 V4 V5 and V6 The aV leads are beneath the standard leads while the chest leads are on the right side

Aneurysm of the basal posterior aspect of the left ventricle may occasionally be visible with a postero anterior chest plate

Often increased rounding of the left ventricle (marked aortic configuration) in a patient who does not have and never had hypertension may point to a cardiac aneurysm (Parkinson et al) If there is a lime salt deposit at an abnormal site along the left cardiac border an aneurysm may be suspected

Even with large aneurysms the diagnosis is often impossible despite careful x ray studies

The electrocardiogram is not characteristic It shows evidence of myocardial involvement and often there are signs of an anterior or rarely of a posterior

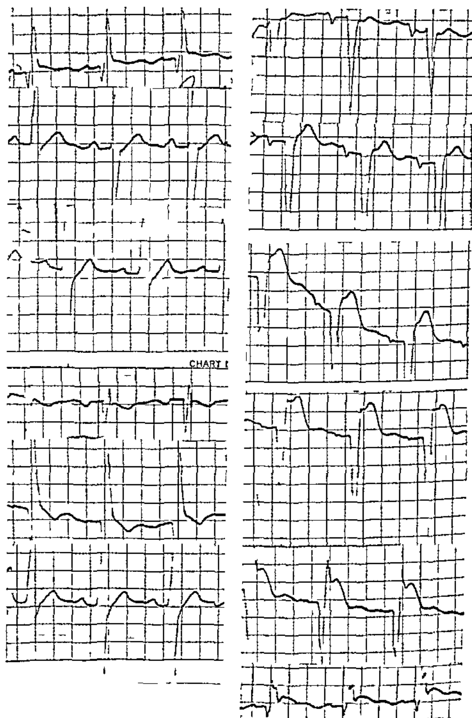


FIG. 76. This electrocardiogram is from the same patient as shown in fig. 7 but was obtained *27 months later. The patient felt well and had resumed medical practice* in spite of his cardiac aneurysm. The RS-T segments in lead I and the chest leads are still elevated. In aVL the T wave remains inverted, while the inversion in the chest leads has disappeared. The patient died 3 years later.

wall infarction In some of our cases a bundle branch block or some of the other changes encountered in coronary disease has been found Many of our patients however showed an unusual persistence of elevation of the RS T segment so that in lead I and in the chest leads one might be inclined to diagnose a recent anterior wall infarction The electrocardiogram shows these features

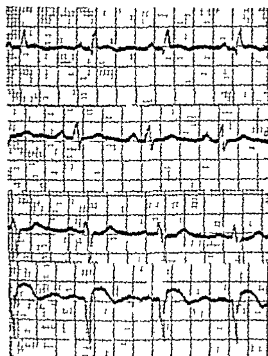


FIG 7 The three standard leads and V 5 of a 70 year old patient with a cardiac aneurysm The clinical diagnosis was confirmed at necropsy Persistent elevation of the RS T segment imitating the pattern of an acute infarction is visible in lead I and V 5 (Courtesy of Dr C Borneman)

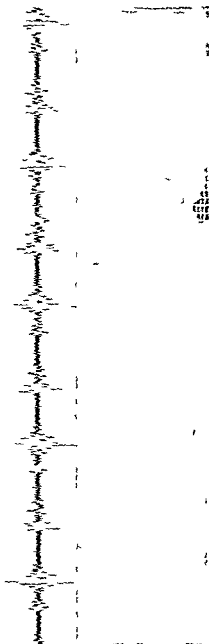


FIG 78 Stethogram of the same patient from whom the electrocardiogram of figure 77 was taken A soft systolic and a louder diastolic murmur are visible (Courtesy of Dr C Borneman)

for many years without further change In our experience if there is a permanent RS T elevation in the electrocardiogram of patients who once had a myocardial infarction the suspicion of a cardiac aneurysm is justified Although this

electrocardiographic pattern is found only in a minority of cardiac aneurysms it is by no means rare

In figures 75 and 76 an electrocardiographic pattern typical for a cardiac aneurysm is reproduced The tracings were obtained from a 56 year old man with a large cardiac aneurysm They show the abnormally deep Q wave with the slight elevation of the RS T segment in lead I and the chest leads

Figure 77 shows the electrocardiogram and figure 78 the stethogram of a patient with a cardiac aneurysm The 70 year old woman showed the typical circumscribed pulsation 16 days after the attack A typical systolic diastolic murmur was heard Postmortem examination revealed an antero lateral wall infarction The wall of the aneurysm was remarkably thin and formed by white translucent fibrous tissue (courtesy Dr C Borneman)

There may be survival of 10 years or more despite a huge cardiac aneurysm One of our patients is active and still free from complaints more than eighteen years after his cardiac aneurysm was recognized Another patient with a cardiac aneurysm which has been present for fourteen years flew over the Atlantic 48 times without any discomfort These patients may lead active lives free from symptoms nevertheless it is clear that physical activities must be curtailed

In many reported cases and in 3 personal observations paroxysmal ventricular tachycardias developed shortly before sudden death in patients with cardiac aneurysms so that one may assume death was the result of ventricular fibrillation

In a patient with a large ventricular aneurysm after infarction the aneurysm has been successfully removed by surgery (Likoff and Bailey)

The Shoulder Hand Syndrome and Dupuytren s Contracture These complications are not infrequent following myocardial infarction They were noted in 17 out of 133 consecutive cases of myocardial infarction (Frnstene and Kinell) They occur most often on the left side that is the side to which pain most often radiates Dystrophy of muscles and a tendency to fibrotic changes appear

Not rarely a patient is alarmed by the development of shoulder pain which he takes to be a sign of a recurrence of angina pectoris But because this pain is independent of physical effort and occurs when the arm is moved distinction is easy Early hyperemia and edema of the hand may appear and last as long as six months This hyperemia like that following trauma leads to osteoporosis Abduction and external rotation of the arm are reduced and tenderness is found on pressure on the periarticular tissues of the shoulder The handicapped patient is unable to use the arm freely The syndrome may appear in patients with exertional angina pectoris or even in asymptomatic coronary sclerosis some time before a myocardial infarction occurs It is occasionally seen 3 to 12 weeks after an infarction in other cases months and even years elapse before it appears Naturally the disturbance is not characteristic of coronary occlusion or an acute infarction It is a common occurrence in coronary sclerosis without angina pectoris and without any evidence of infarction

Many attempts have been made to explain these changes Viscero visceral reflexes reflex vascular spasm in the periarticular tissue and resultant nutritional disturbances have been suspected to be determining factors

At the present time it is assumed that afferent stimuli from the heart bombard the internuncial pool which is a network of interconnecting neurons in the central grey matter extending over several segments in the spinal cord From here outgoing stimuli influence autonomic pathways

The disability and pain may last for six months and may recur at any time

It is claimed by some investigators that this syndrome appears particularly in subjects with a certain type of personality that is in those who tolerate pain poorly (Coventry) The process is said to progress faster if the arm is not used

If procaine is injected into the stellate ganglion in the early stages of the syndrome rapid recovery may occur or progression is prevented Cortisone has also proved useful A dose of 75 mg is given daily and with the appearance of improvement the amount is reduced to 50 and then 25 mg Hydrocortisone 50 mg injected into a trigger zone only once is said to help many patients (Berger)

Combined with or independent of these shoulder affections changes may also be noticed in the left (rarely the right) hand The skin is glossy and the hand as well as the fingers become stiff the patient is unable to bend the hand or to make a fist A slight red discoloration appears and the fingers are cold The ulnar side is affected more than the rest of the hand Atrophy of the skin follows These changes were noted in 39 (21 8 per cent) out of 178 consecutive cases of myocardial infarction (Johnson) They may develop as early as three weeks after the infarction Gradually the picture of Dupuytren s contracture develops The lesion may be symmetrical and independent of the site of radiation of the pain

Dupuytren s contracture does not seem to be an entity but may follow any irritation of the sympathetic nervous system It occurs in diverse visceral diseases Here also the possibility of reflex vasoconstriction has been discussed

There is no sharp distinction between these conditions and Sudeck s atrophy and causalgia

DIFFERENTIAL DIAGNOSIS

In the preceding sections it has been pointed out that coronary occlusion with myocardial infarction may cause a series of symptoms and signs which readily permit the diagnosis in a vast majority of cases Occasionally however as the result of absence of pain or of abnormal radiation of the pain or due to the fact that pain similar to that observed in coronary occlusion occurs in other diseases the diagnosis is missed In addition certain signs arise due to complications thereby further confusing the clinical picture Moreover now that physicians are more coronary conscious the diagnosis of occlusion with infarction is made at times when the condition is not present

At this juncture it must be re emphasized that the diagnosis should never be made on the basis of the pain alone Even if the pain is typical' lasts for hours is overwhelming in intensity or radiates to the left arm and hand another condition may be present The diagnosis should always be confirmed by one of the signs mentioned previously — elevated temperature fall of blood pressure increased sedimentation rate and so forth On the other hand every complaint of pressure or tension behind the sternum irrespective of how slight it is should arouse the suspicion of the presence of a myocardial infarction when the distress lasts for longer than a few minutes

Epilepsy In patients with many successive attacks of epileptic convulsions or status epilepticus the violent effort caused by tonic and clonic convulsions without adequate breathing causes hypoxia of the heart muscle and myocardial necrosis Neuberger found such necroses in 14 of 34 patients

One must remember on the other hand that patients with myocardial infarction may develop Stokes Adams attacks resembling epileptic convulsions The differential diagnosis must be considered and will usually be possible

Cardiac Neurosis Pain in the cardiac region is common in cardiac neuroses (see neurocirculatory asthenia) In contradistinction to coronary thrombosis the pain is often shortlasting and stabbing although it may be prolonged and severe In this instance it is usually located at the cardiac apex and not behind the sternum The patient indicates the painful area by pointing with the tip of a finger rather than the palm of the hand as in anginal pain of any etiology Occasionally a circumscribed area at the apex will be sensitive to pressure The frequent recurrence of this pain its relation to certain emotional disturbances the absence of organic findings and the presence of the signs of a cardiac neurosis usually permit the diagnosis Occasionally a cardiac neurosis of this type develops after a friend or relative suddenly and unexpectedly died in my arms from a coronary attack

Sensations of an unpleasant character are often noted in the cardiac area by healthy people who may recognize the relation to emotions anxiety and the like While they rarely gain importance and are not associated with heart disease by the average healthy person they may become major problems in anyone who is apprehensive and readily alarmed

It does not seem amiss to stress that very careful examination and observation are necessary before a patient is labeled neurotic The information some patients obtain from pseudoscientific publications in magazines and newspapers occasionally makes it difficult to secure an unbiased history

The Thoracic Cage and Spondylarthritis Osteoarthritis of the upper dorsal vertebra causes distress that is frequently confused with the pain of coronary disease The pain may last for seconds or hours it has the typical radiation to the left or right arm and it may be very distressing Usually there are no objective findings the movements of the upper dorsal vertebrae are sometimes restricted The spinous processes of the first dorsal vertebrae are occasionally sensitive to percussion and a segmental cutaneous hyperesthesia is sometimes

demonstrable X ray demonstration of a hypertrophic spondylitis is diagnostically indecisive since such evidence is secured very often in adults without symptoms On the other hand there may be an extensive hypertrophic osteoarthritis with negative x ray findings

Similar attacks of pain with the same radiation occur in myositis and fibromyositis of the long dorsal muscles in the other thoracic segments

Radiculitis of the upper dorsal spine may cause pain which contrary to some statements may be retrosternal It appears particularly when the patient assumes a certain position in bed and is relieved when the position is altered It also occurs with coughing straining at stool and sneezing At times it appears while the patient is walking and swinging his body here the differential diagnosis from an exertional angina is especially difficult Pressure on the spine or percussion of the spinous processes may reproduce the pain It is noted particularly often in patients with deformities of the spine Certain trigger points release the pain Cases have been observed in which nitroglycerin afforded relief thus making the diagnosis even more difficult

The occurrence of pain that radiates into the left or right arm in these lesions has been clarified by the important work of Lewis and Kellgren by injection of a hypertonic saline solution into the interspinous ligaments and adjacent muscles they produced in the corresponding segments the same type of pain with similar referred phenomena as found in visceral disease If such injections are made into the upper thoracic segments in patients who had a myocardial infarction at some earlier date they produce pain indistinguishable from that of an angina pectoris in myocardial infarction Even the upper chest may feel constricted the retrosternal pain however is missed in such experiments

The differential diagnosis often is very difficult particularly in early stages and problems arise when the pain is so severe that respiration is rendered difficult The situation becomes more apparent after the symptoms have existed for a time and cardiac findings remain negative In this instance as with the cardiac neuroses careful examination and observation over a period are necessary before a positive diagnosis can be made

It is important to note that in some cases of spondylarthritis the pain may be retrosternal and increases or appears on exertion owing to abnormal strain on the somatic structures involved In these cases injection of novocaine into the interspinous ligaments and adjacent structures provides immediate relief X ray radiation of the spine is helpful and most beneficial in chronic cases

In patients with intercostal neuralgia herpes zoster neuralgia of the brachial plexus or a myositis in the corresponding segments the history may be somewhat similar to that of a coronary occlusion but a careful examination usually permits differentiation In the first hours before the herpetic eruption appears however the diagnosis may be difficult since negative cardiac findings can be encountered in cases of coronary occlusion An important and common

type of pain in women with endocrine disturbances will be discussed in the appropriate section

Pulmonary Embolism As pointed out before this event occasionally provokes a syndrome very similar to that of myocardial infarction In both conditions there may be the same prolonged pain the same radiation and localization Fall of blood pressure leukocytosis fever increased sedimentation rate hemoptysis pericarditis and even similar electrocardiographic alterations are observed in some patients The differential diagnosis may be difficult or impossible The task of distinction is rendered harder by the fact that many patients with myocardial infarction develop a peripheral venous thrombosis owing to the enforced rest in bed and the disturbance of circulation The so called second attack which develops a few days or weeks after coronary occlusion is due in many cases to a pulmonary embolus although the symptoms may be almost identical to those experienced during the development of the myocardial infarction In all attacks of this type that appear in bedridden patients pulmonary embolism should be suspected The differentiation is easier if the electrocardiogram shows the typical pattern of myocardial infarction or pulmonary embolism respectively In both conditions however occasionally only indefinite changes appear The absence of an increase of transaminase in the blood speaks for pulmonary embolism But positive tests in pulmonary infarction have been reported

Pneumonia If the patient does not have much anginal pain but dyspnea fever and rales over circumscribed areas of the lungs are present the diagnosis of pneumonia is sometimes made Formerly this happened frequently but now the mistake is unusual In a similar way a left sided pleuritis was often diagnosed and the provocative infarction overlooked

Spontaneous Pneumothorax This and spontaneous mediastinal emphysema may cause prolonged severe retrosternal pain with radiation toward the shoulders but the differential diagnosis is easy

Gastrointestinal Disease *Many disturbances of the gastrointestinal tract* may simulate coronary occlusion Esophageal spasm may cause excruciating pains often situated behind the lower sternum It may spread to the jaw or into the arms lasting for hours Some patients report benefit from nitroglycerin In others only a dull ache is experienced Retrosternal pain occurring at night and often sufficiently severe to require demerol or morphine for relief is sometimes noted in carcinoma of the esophagus Since dysphagia may be minimal or absent in these cases and the attack does not occur in connection with eating prolonged episodes may lead to the erroneous diagnosis of actual or impending coronary occlusion

It is very common to note severe pain radiating to or perceived only in the left chest or shoulder in colonic spasm Distention of the splenic colon can cause precordial pain and pain spreading into the left arm The pain noted in connection with these colonic disturbances may be severe and prolonged Peptic ulcer cholelithiasis and cholecystitis occasionally present pain that is located exclusively

in the chest if this pain happens to be felt only on the left side the diagnosis of a possible coronary disease may arise

Gallbladder Disease The incidence of gallbladder attacks is greater in patients with coronary sclerosis than in the general population The fact that gallbladder disease and myocardial infarction may coexist creates a difficult diagnostic problem in some patients An attack may begin as a typical gallstone colic and in the convalescence or following surgery myocardial infarction may follow

In gallstone colic the pain may be substernal and may radiate into both arms

Damage to the heart from gallbladder disease has frequently been mentioned The disappearance of arrhythmias following removal of the gallbladder has been reported but such statements must be accepted with considerable reservation

Jaundice temperature leukocytosis and tenderness in the region of the gallbladder (liver) follow a gallstone attack as well as myocardial infarction

Of greater importance on the other hand is the fact that a variety of gastrointestinal symptoms appears in patients with myocardial infarction If the anginal pain happens to be slight or absent mistakes are possible

It is common knowledge that a cardiac infarction may simulate an acute abdominal condition This was clearly demonstrated in early clinical observations on this condition when the occurrence of a status gastralgicus was emphasized The pain in coronary occlusion may be exclusively abdominal If it is so intolerable that the patient is unable to move — if the abdominal muscles are rigid and there is associated shock and vomiting — the diagnosis of a perforated peptic ulcer or pancreatic necrosis is comprehensible Physical examination of the heart may disclose nothing abnormal despite a large myocardial infarction other methods of investigation such as the electrocardiogram or x ray (to detect a bubble of gas beneath the diaphragm) may not be available and such patients have undergone surgery

Sometimes laparotomy appears necessary but physicians refuse to operate because the patient reported some cardiac symptoms of long duration and because positive cardiac findings were present accordingly the diagnosis of coronary occlusion with abdominal symptoms seems logical At necropsy peritonitis associated with a perforated peptic ulcer was found We have seen single cases of a combined coronary occlusion and perforated ulcer and one of coronary occlusion and acute hemorrhagic pancreatitis

As an aid to differential diagnosis it may sometimes be helpful to remember that cardiac infarction with abdominal pain does not cause the boardlike rigidity of the patient with a perforated viscus on the other hand a closed perforation may also fail to present this rigidity

If pain is experienced only in the right upper abdominal quadrant cholelithiasis may be suspected if fever leukocytosis hepatic enlargement and jaundice develop cholecystitis is often diagnosed

Confusion with acute gastritis or gastroenteritis is less common than even fifteen years ago If pain was absent or slight and localized in the epigastrium

while nausea vomiting and diarrhea (due to visceral reflexes) were in the fore ground acute indigestion *was a common diagnosis Sudden death due to* overeating or to acute dilatation of the stomach so often described in older literature was usually due to coronary occlusion

Esophageal Hiatus Hernia This abnormality causes a syndrome that is easily confused with coronary disease and coronary occlusion Three forms of this disturbance which is most common in obese women who are stocky in build and who have had several children are known First the congenitally short esophagus formerly considered common and now regarded as rare if indeed existing at all Second para esophageal hernia which is a true hernia Here the anterior part of the fundus rolls into the chest in front of and lateral to the esophagus (rolling hernia) The sphincter action of the esophagus is intact Third the sliding hernia or esophago gastric hernia, which represents the most common type In this instance perhaps owing to a defect of the diaphragm reflux of food and acid from the stomach occurs Esophagitis appears with easy bleeding from the inflamed mucosa Shrinking of the connective tissue and scar formation make the esophagus appear shorter and part of the cardiac portion of the stomach appears in the chest

Nuzum found a hiatus hernia in 12 27 per cent of 957 persons examined He found it in 25 per cent of patients with true angina pectoris Thus the two conditions may and often do coexist

There are all variations between no complaints at all and excruciating crippling pain not rarely retrosternally and spreading to the jaw or both arms Pains occur at night

Symptoms may appear at any age but most patients are beyond 40 years Fullness during or shortly after meals regurgitation belching hiccough nausea and vomiting are common All these complaints however are also found in coronary disease and myocardial infarctions

About one third of the patients complain of substernal pain This pain may radiate into the left shoulder and even into the left arm Belching may give immediate relief Considerable anxiety and distress may be present Sometimes the pain appears on exertion and is relieved by nitrites (Jones) According to Donnelly contraction of the abdominal muscles on walking increases intra esophageal pressure and this leads to pain in patients with esophagitis Pain on stooping is common for similar reasons The patient may feel particularly uncomfortable at night and often experiences the nocturnal distress while lying in bed immediate relief is secured by standing This point in the history is rather characteristic

The diagnosis is often confirmed by x ray examination which should be made in the Trendelenburg position Often however the hernia does not appear on tilting but is demonstrated when the patient bends forward Roentgen examination may be temporarily negative

Electrocardiographic changes appear (Cossio and Fustinoni Kaiser) which like the pain have been explained by reflex changes in the coronary blood flow

or have been initiated by mechanical irritation of the vagal fibers in the esophageal hiatus However since the lower esophagus derives its sensory innervation from the fourth to sixth thoracic segments the pain may be truly referred The rapid response to nitroglycerin and the changes in the electrocardiogram seem to favor the first explanation

Treatment is surgical in some cases The administration of alkalies and the use of frequent small feedings of a bland nature are usually recommended and sometimes help Phrenic crush may give relief

Peptic ulcer frequently develops at the level of the esophageal hiatus if it bleeds the patient may suffer from severe anemia

Internal Hemorrhage Patients with an acute and profuse hemorrhage from a peptic ulcer or cirrhosis of the liver may present a syndrome of prolonged sudden severe anginal pain with radiation to the left arm shock and collapse In 16 out of 18 such cases very distinct changes were demonstrable in the electrocardiogram (Scherf et al) therefore the differentiation from coronary diseases may be difficult Mistakes are particularly liable to occur when there is no hematemesis and when the appearance of tarry stools is delayed for two or three days A marked anemia also need not be present since the acuity of blood loss rather than its quantity causes the symptoms and the electrocardiographic changes

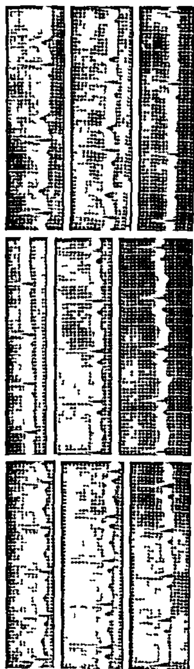


FIG 19 A series of tracings from a patient with an acute profuse internal hemorrhage (the three standard leads are beneath each other)

General vasoconstriction occurs following blood loss and involves the arteries as well as the veins there is an adjustment of the vascular bed to the diminished amount of blood (Bazett) This seems to be effected by carotid sinus reflexes when the arterial blood pressure shows a tendency to fall and by reflexes from the veins There is

a general vasoconstriction following a fall in venous pressure (McDowall reflex)

For a long time it was believed that this homeostasis was necessary to protect vital organs like the heart from a reduced blood supply The frequent finding of electrocardiographic changes after an acute blood loss shows however that the coronary arteries participate in the general vasoconstriction The anginal pain disappears in a few hours and the changes in the electrocardiogram vanish in a few days even if there is no improvement in the status of the red blood cell count

In figure 79 electrocardiograms in the three limb leads are reproduced These were taken from a 32 year old male who was admitted for an acute hematemesis from a duodenal ulcer Figure 79a shows the electrocardiogram obtained immediately after admission i e about six hours after hemorrhage It shows only a sinus tachycardia The second electrocardiogram registered about 20 hours after the hemorrhage shows abnormal T waves in each lead The third tracing was obtained five days after the first one and is normal

It seems that the changes appear not earlier than 6 or 7 hours before and not later than 18 to 20 hours after the hemorrhage They disappear in a week to 10 days

If the myocardium of an animal is examined following an acute blood loss necrosis in the subendocardial layers is found which is typical of a diminished blood (oxygen) supply to the heart

The occurrence of coronary thrombosis in patients with coronary sclerosis has been observed following an acute internal hemorrhage

Blindness following hematemesis or other forms of hemorrhage may also be explained by the reflex vasoconstriction (Black Levatin)

Acute Pericarditis It was noted earlier that this lesion is sometimes associated with severe precordial pain which lasts for hours Since the epicardium and a great part of the parietal pericardium are insensitive to painful stimuli some have assumed that irritation of the sensory fibers at the base of the heart where the epicardium reflects into the pericardium accounts for the pain Mediastinitis is a more probable cause If this pain is present in a patient with pericarditis it may be difficult to decide whether a tuberculous rheumatic or pneumococcic pericarditis is present or a pericarditis following myocardial infarction The electrocardiogram often but not invariably offers assistance in the differentiation

Other Causes Frequently severe pain occurs in an attack of paroxysmal tachycardia during a hypertensive crisis and in women with disturbances of ovarian function as will be discussed later These conditions may also be confused with the pain of myocardial infarction

The difficulty of differentiation between myocardial infarction and dissection of the aorta will be discussed later in the book

PRODROMAL SYMPTOMS

In a large percentage of patients there are no symptoms before the appearance of coronary occlusion and myocardial infarction The first attack strikes like lightning

Some patients have had an angina on effort for years These patients may develop the prolonged pain due to myocardial infarction suddenly and without premonitory signs In others however the imminent threat of coronary occlusion can be predicted in this group attacks begin to appear at rest they last longer are more severe and nitroglycerin affords progressively less relief Under these circumstances it is wise to keep the patient quiet and to take the necessary steps for the imminent emergency (administration of vasodilators) Patients with prodromal symptoms are not rare The classic picture of myocardial infarction need not develop however because a slow and painless fibrotic occlusion may develop or collateral circulation may become active and prevent an infarction even in the presence of a coronary occlusion

Some patients who develop a myocardial infarction describe some minor attacks they had — a few days prior to the major episode — that lasted for only a few minutes these attacks were so slight they were disregarded

PROGNOSIS

If a coronary thrombosis has occurred sudden death may follow at any given subsequent moment Sudden death is also common in coronary sclerosis and coronary involvement secondary to aortitis In a series of 198 instances of sudden death coronary disease was demonstrable in 104 at necropsy valvular diseases and various kinds of aneurysms were next in order (Bedford)

Formerly the immediate mortality of the first attack was regarded as much higher (53 3 per cent) (Levine and Brown) than at present (10 to 15 per cent) Some authors report an immediate mortality of only 10 per cent which would agree with our experience in patients who survive the first few hours Statistics of this kind necessarily depend upon the material patients who die suddenly before a physician is called or even before uttering a complaint are not included in statistics Statistics also depend upon a definition of the word immediate Among U S soldiers under 40 years of age Yater et al found an immediate death in 16 per cent death in 15 minutes in 10 per cent An additional 5 per cent of the patients died within 2 hours Among the patients who reached the hospital 18 per cent died within 24 hours and 12 5 per cent later

The causes of death are ventricular fibrillation shock cerebral emboli congestive heart failure and cardiac rupture The first three weeks are particularly precarious

The prognosis is worse as pointed out earlier if extrasystoles or paroxysmal tachycardia appear if the systolic blood pressure falls below 80 mm Hg if there is severe dyspnea and pulmonary congestion or early shock The mortality in the first attack seems to be greater if the patients were previously hypertensive

and the prognosis in the second or third attack of myocardial infarction is worse than in the first one

On the other hand a patient often recovers to such an extent that he leads a normal life for years without complaints The average duration of life in a series of 101 cases (Rosenbaum and Levine) was 41 months One fourth of these patients died within a year one half within two years and three fourths within five years The status of the other coronary arteries is decisive for the outcome We believe that the figures would be more encouraging if all infarctions occurring in practice were included

In one observation a patient had his first attack of coronary thrombosis when 40 years old and the second when 75 years old A third attack occurred in his seventy eighth year The patient died at 80 nearly 40 years after the first attack (Drake)

Instances of myocardial infarction in pregnancy with successful delivery are known (Antonius et al) However many patients succumb

Sooner or later a large number of patients develop left ventricular failure and pulmonary engorgement A large percentage of patients who do not have exertional anginal pain prior to the attack have pain even in bed after the episode and are particularly apt to complain of anginal pain on effort

It seems advisable to stress once again that patients with coronary disease even if their condition seems satisfactory may present very serious complications or may succumb suddenly at any moment but there are cases on the other hand in which the patients were unconscious with unbelievably low blood pressures and almost inaudible heart sounds who recovered and lived normally for many years

Accordingly the prognosis should never be regarded as good even when the patient has a very light attack and seems well off on the other hand it should never be absolutely hopeless There are few cardiac conditions in which the unexpected happens more often Surprises are encountered in both directions

TREATMENT

General Measures Not only physical but also mental rest is important The patient is put at ease and is reassured he is told that he had a vascular spasm in the heart (the word thrombosis is avoided) From the beginning he is examined and controlled constantly as if he were in a diabetic coma A simple light case might become an emergency at any moment Later he is examined at least twice and then once daily Even the excitement of ward rounds may cause a fatal accident (Jarvinen)

Pain The severe anginal pain accompanying an acute coronary thrombosis requires demerol or morphine (or pantopon) The initial dose of morphine should be 0 015—0 02 Gm and it is well to add some atropine (0 5 mg) to the first injection of morphine sulfate In many cases it will be necessary to follow the first injection after 30 minutes with a second or even third occasionally even

this fails to relieve pain We have seen patients toss restlessly and complain bitterly about excruciating pain after having received more than 0 06 Gm of morphine within three hours Demerol causes less side effects and less respiratory depression and is preferred In these cases phenobarbital affords little relief infiltration of the skin in the area to which the pain is referred has been recommended but provides no relief in our experience Paravertebral anesthesia helps immediately but is rarely done because one always hopes that the pain will disappear in the next hour The distress may persist however with unabated intensity for 24 hours or more and may exhaust the patient completely

Oxygen Persistent pain threatening shock arrhythmias and even marked fall of blood pressure are indications for the administration of oxygen With a nasal catheter and a flow of 5 to 6 liters per minute the concentration reached is only 30 per cent With a tent and a flow of 12 to 13 liters the concentration is 40 to 50 per cent It reaches 70 per cent with a mask and is given for 5 to 6 hours and then removed for short intervals The patient who is frightened by the suggestion of oxygen is reassured and told that it takes the load off the heart It is wise not to wait until complications develop but to administer oxygen for the first few days in every patient when the evidence speaks for the presence of a larger infarction

Anticoagulants The use dosage indications and contraindications of anticoagulants have been discussed in a preceding chapter At this point it is appropriate to discuss their use in patients with myocardial infarctions

In myocardial infarction danger arises from both intracardiac thrombi which may cause systemic embolism and thrombi formed in the peripheral veins which produce pulmonary embolism during the period of rest Because of the high incidence of these complications and the discovery of hypercoagulability of the blood after an infarction the Committee of the American Heart Association under the Chairmanship of I S Wright has recommended treatment with anticoagulants in all cases of coronary thrombosis with infarction unless such therapy is contraindicated This recommendation is based upon the experience gained from over 1000 observations It was found that thromboembolic phenomena appeared in 41 8 per cent of the control (untreated) subjects while they appeared in only 13 1 per cent of the treated cases Among the controls 23 4 per cent died within 6 weeks while in the treated group only 16 per cent died These differences are statistically significant even if one considers that an occasional patient may die from consequences of therapy and that the percentage of cardiac rupture and pericardial hemorrhage is 2 per cent of untreated cases and 4 per cent of treated ones The value of anticoagulants was particularly evident in obese patients and those with congestive heart failure

Lately it has been recommended that only the severely ill (poor risk) patient be treated with anticoagulants and that these compounds be omitted in the mild (satisfactory) cases This seems to be the current attitude of most cardiologists in this country In our opinion however this attitude is not justified As stated earlier a clinically mild case may suddenly turn into a severe one

the appearance of thromboembolism in mild cases can never be predicted Actually those who have seen a mild case recovering nicely suddenly develop cerebral embolism resulting in a permanent hemiplegia or a peripheral embolism necessitating amputation of one leg will be hesitant to treat only severely sick patients with anticoagulants Good risk patients exist only in retrospect (Gilchrist and Tulloch) One must always keep in mind that the administration of anticoagulants does not abolish but merely reduces the danger of thrombo embolism while at the same time adding new dangers the possibility of hemorrhage and cardiac rupture with hemopericardium

It has been claimed that in patients with myocardial infarction treated with anticoagulants cardiac failure is less common and recovery from shock occurs more readily

One of the disadvantages of therapy with Dicumarol or similar compounds is that according to the investigations of Wright s Committee no satisfactory preventive effect is accomplished unless the prothrombin time is kept at levels between 25 and 39 seconds This is difficult to establish prothrombin times of over 30 often lead to bleeding We try to keep the patient s prothrombin time at double the control value

The treatment is not applicable to patients with blood dyscrasias bleeding ulcers hypoprothrombinemia (vitamin K deficiencies liver damage) renal damage and insufficiency anemias of various etiologies late pregnancy open wounds subacute bacterial endocarditis and postoperative drainage of viscera

Most physicians do not give heparin at the beginning Therefore the patient often remains unprotected for the first few days in which most thrombi form The administration of heparin should start immediately after the diagnosis is made if the patient is to be protected as far as possible If future investigations show that injection of concentrated heparin (1 ml containing 100 mg) every 12 hours protects the patient from thrombus formation even during the period when the coagulation time returns to normal before the next injection is due a relatively safe method will be available We prefer this procedure at the present time

It is often stated that anticoagulant therapy should be given for 21 to 30 days In our opinion such treatment should be continued until the patient is fully ambulatory In order that rebound phenomena be prevented the dose is gradually diminished over a few days instead of therapy s being discontinued abruptly

Nichols used anticoagulants as a prophylactic measure over a period of years in patients who had recovered from one attack and it was recommended in patients with the premonitory syndrome when an attack threatened Our experience concurs with that of others — we believe that this therapy should not be used Since rupture of giant capillaries in the atherosclerotic area of the coronary artery is a frequent cause of coronary thrombosis this treatment may be harmful in four patients with the premonitory syndrome we observed coronary occlusion following soon after such therapy Nic s himself is very

cautious in his conclusions In some publications in which this treatment is recommended as a good prophylaxis the published electrocardiograms show that the patients had infarctions during the therapy that had not been recognized by the authors It has been found however that the mortality rate of those patients in whom preventive long term anticoagulant therapy was used is lower (Suzmann et al)

Of all investigators pleading against therapy with anticoagulants no one is more articulate than Evans Let it go now before remorse weighs too heavily on those who may continue for a little longer to advocate its use

Shock When shock is impending the patient should be hospitalized He should be placed in the horizontal position and administered oxygen One should examine the patient carefully for evidence of cardiac failure (pulmonary congestion engorged neck veins) which may be present simultaneously and which needs special therapy Demerol should be administered It is evident that in the presence of or with impending pulmonary edema the intravenous administration of blood or plasma may be injurious

Success has been reported from the intravenous or intraarterial infusion of blood plasma or plasma substitutes When shock occurs because of a diminished cardiac output that results from direct cardiac damage success should not be expected indeed often harm will be done It is recommended that more than 300 ml of plasma or blood not be administered despite the fact that some authors advocate as much as 1000 ml The rate of infusion also varies some recommend not more than 2 ml per minute while others permit 100 ml per minute For the intraarterial infusion the exposed radial artery is used

The best plasma substitute is dextran recommended by Swedish workers It is a polysaccharide obtained through enzymatic action with a molecular size similar to that of plasma proteins Dextran has little pyrogenic or antigenic action and is very slowly excreted without being metabolized therefore it circulates in the body for days

Pressor amines have been used for years especially neosynephrine which has the advantage of creating fewer arrhythmias than epinephrine It is given hypodermically or intramuscularly (10—15 mg) and is repeated as often as necessary that is whenever the blood pressure falls In recent years the effect of norepinephrine has been widely studied Most authors advise its use since in small doses it has predominate effect on the peripheral vessels while the cardiac effect is minimal Norepinephrine also raises cardiac oxygen consumption much less than epinephrine and it causes fewer dangerous ventricular arrhythmias than epinephrine although this action is not completely absent as some claim In some animals norepinephrine widens the coronary arteries its action in man is unknown The disadvantage of the substance is that it must be given in an infusion one ampule (4 mg) is diluted with 500 cc of saline or 5 per cent glucose First administration is 10 drops per minute the dose is then regulated according to the blood pressure and the appearance of arrhythmias In recent years isopropylarterenol (Isuprel) has been used (10 mg) For quick action

linguets are available Wyamine (mephenteramine) is given in doses of 15–30 mg intramuscularly as often as necessary

In one patient 402 mg of Levophed were given during a period of 14 days The patient recovered (Siglin)

Dehydration This condition with all its attendant dangers is common and results from the vomiting and profuse perspiration The physician in charge must avoid the administration of large amounts of fluid because of the danger of pulmonary edema Hypodermoclysis is often necessary

Vasodilators It is useful to administer vasodilators early because the fate of patients depends to a great extent on the function of the collateral circulation We prefer slowly released nitroglycerin e g Nitroglyn (gr 1/10) The experiments of Zoll and Normann demonstrated the significant effects of nitrites in the creation of functioning interarterial coronary anastomoses Papaverine hydrochloride and aminophylline are also recommended Neither drug should however be given intravenously to patients with acute coronary thrombosis In therapeutic doses papaverine is harmless for a healthy and even a slightly damaged myocardium but the effects are quite different if large doses are given intravenously to a patient with a damaged heart Experimental studies on the cardiac action of papaverine in patients with damaged hearts are scarce Our clinical experience with intravenous injections of papaverine in patients with a fresh coronary occlusion is not satisfactory but there is no objection to an intramuscular injection of 0 04 to 0 06 Gm Likewise aminophylline should not be given intravenously to patients whose blood pressure shows a tendency to fall Since intramuscular injections are usually painful a rectal suppository of 0 5 Gm of aminophylline should be inserted twice daily

While we consider aminophylline to be one of the most effective vasodilators available it should be pointed out at this juncture that on the basis of experimental studies purine bodies (caffeine theobromine) particularly theophylline increase the coagulability of the blood The coagulation time may be shortened by 50 per cent Lately it has been found that these substances in a dosage equivalent to that given in man cause hyperthrombinemia Since clinical investigations confirm these results serious objections must arise against the use of theobromine caffeine and theophylline in patients in whom the danger of thrombus formation exists For a time our results were not confirmed Recently in Seegers laboratory it was found that Ac globulin which tremendously enhances *the conversion of prothrombin into thrombin is increased in the dog* by more than 100 per cent by aminophylline The dose however is large — 0 1 Gm per Kg Seegers also reports that larger doses of Dicumarol are necessary if aminophylline is given simultaneously (McCormick and Young) In a few cases of coronary sclerosis with angina pectoris we observed coronary thrombosis following intravenous injections of aminophylline

Quinidine Another emergency measure is the administration of quinidine We give 0 2 Gm every four hours routinely to all patients with a fresh coronary occlusion to prevent dangerous extrasystolic disturbances of rhythm If extra

systoles occur in spite of this regimen the dose may have to be increased (figure 80) If a paroxysmal ventricular tachycardia complicates coronary thrombosis doses up to 2 0 Gm of quinidine sulfate daily may be necessary The danger of a tachycardia in a case of recent myocardial infarction is greater than the possible harm which might be caused by larger doses of quinidine

The present custom not to treat prophylactically with quinidine but to use the drug only immediately when extrasystoles appear is strange It is based

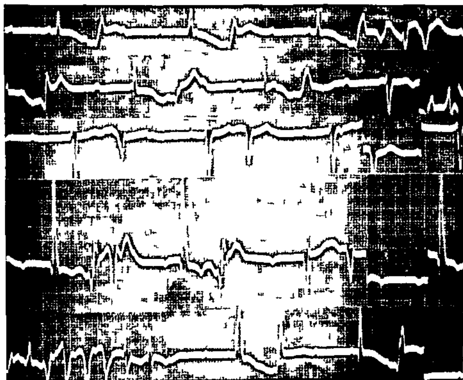


FIG 80 In a 59 year old man with a myocardial infarction complete heart block appeared with massive inversion of the T waves Multiple multiform ventricular extrasystoles appeared These are the extrasystoles which often precede ventricular fibrillation Occasionally abnormal ectopic idioventricular beats are also visible

mostly on experiments on animals which are not comparable to clinical cases of coronary thrombosis for two reasons One is the fact that dogs (on which many experiments were done) develop ventricular fibrillation in 30 per cent of the cases after ligation of the coronary arteries When quinidine therapy that is started prior to ligation in such animals fails to diminish the incidence of fibrillation it may be because of overwhelming impulses Man may respond differently Actually extrasystoles that appear following coronary occlusion disappear in man quickly if quinidine is given in most instances

A second reason for the lack of correlation between animal experiments and clinical cases of coronary thrombosis is that in most experiments quinidine was given intravenously in such doses that apnea and diastolic cardiac standstill occurred This explains why in some statistics the mortality in animals who received quinidine before ligation of the coronary arteries was even higher than in the controls

In a clinical investigation Boone and Pappas found a mortality of 16 per cent in patients with myocardial infarction who received 0 2 Gm of quinidine every 3 hours while awake The mortality in 127 untreated subjects was 35 per cent

Other Measures Nitroglycerin is given if temporary attacks of anginal pain recur

For patients with heart block temporary cardiac standstill and attacks of Stokes Adams syndrome the administration of aminophylline in the form of suppositories usually suffices Occasionally 30 mg of ephedrine must also be given three times a day in this group of cases to prevent new attacks of Stokes Adams syndrome Linguets of isoprel are also useful

Bed Rest Often absolute rest cannot be enforced during the acute pain for the patient may feel compelled to move by anxiety and restlessness When the pain eases and patients have less pain from the start strict bed rest is ordered The patient is told to lie quietly on his back and to avoid turning from side to side the main objective is to relieve every possible strain on the heart since movement may increase cardiac activity Even during the period of strict bed rest the patient is advised to wriggle the toes (venous thrombosis often begins in the sole of the foot) and to bend the knees slowly from time to time and keep them bent for a while if the condition forbids active moments an attendant should perform passive exercises by bending the lower extremities at the hip and knee joints This should be repeated often during the day and should begin immediately after bed rest is enforced in order to lessen the incidence of thrombosis in the lower extremities and the pelvic veins Slight elevation of the lower end of the bed is useful and the application of an elastic bandage on the lower legs is indicated in order to speed up blood flow in the deeper veins

All these measures warrant careful consideration if the common and serious complication pulmonary embolism is to be averted

Recently chair treatment was recommended by Levine In this therapy the patient is permitted to sit in a chair within the first few days after an attack While the procedure need not be harmful in cases of little infarctions it is certainly dangerous with large ones It must be pointed out that among 115 consecutive necropsies performed on patients in a mental institution 16 of 22 cases with myocardial infarction died of cardiac rupture (Jetter and White) This is the type of patient who does not rest in bed after an infarction

The risk of thrombosis of the veins of the leg and pulmonary embolism is increased when patients sit quietly in the chair for hours This danger threatens even if anticoagulants are given

In other investigations it was recommended that a commode be used instead of a bedpan The oxygen consumption with the use of a commode was found to be less than with a bedpan from this it was concluded that with the former less energy is expended Patients who used the bedpan however were advised to perform the Valsalva experiment (i e to force) a procedure which no patient with an acute or old infarction should ever be permitted to do this effort increases the oxygen consumption

In patients with prostatic hypertrophy bed rest may lead to urinary retention which should be taken care of

Mental rest must also be enforced Telephone calls visitors and other disturbing influences should not be permitted

The period of absolute bed rest should last at least three weeks for patients with a marked fall of blood pressure distant heart sounds, pulmonary congestion gallop rhythm or tachycardia If clinical findings are satisfactory strict rest is enforced for only 10 days After this period permission is granted for the patient to turn slowly on one side or the other Not until five weeks pass however do we allow the patient to sit up in bed and in severe cases the period of continuous recumbent position is prolonged until the clinical findings are satisfactory Sometimes low blood pressure muffled almost inaudible heart sounds tachycardia and the tendency to congestive heart failure compel one to insist on a much longer period of bed rest We have repeatedly seen patients whose condition during a period of six to eight months did not justify granting permission to leave the bed In one of our patients bed rest for 11 months was necessary before improvement was regarded as sufficient This patient has been active despite the development of a cardiac aneurysm and has been free from symptoms for ten and one half years

If however in patients who suffered even from severe pain the fall of blood pressure later is only moderate the heart sounds remain loud and the sedimentation rate is only moderately accelerated the bed rest may be shortened to about three weeks This is common in anterior wall infarction or infarctions without changes of the QRS complex in the electrocardiogram In little infarctions to be discussed below bed rest of 7 to 10 days suffices and bathroom privileges are permitted from the beginning of convalescence

It should be stressed once more that the clinical impression is more important than the laboratory findings in making the decision with regard to the maintenance of bed rest While connective tissue appears in the necrotic area in a few days firm healing requires at least eight weeks (Karsner and Dwyer Mallory et al) The electrocardiogram may show progressive improvement even four to eight months after the attack

In a large infarction when the time for bed rest is over the patient is permitted to sit up in bed at first only for a few minutes but gradually for longer periods after a week he is allowed to dangle the legs About two weeks from the day he first sat up in bed the patient may sit in an easy chair near his bed Another week elapses before the patient may walk freely about his apartment

or room With the gradual restoration to normal activities under continuous observation highly satisfactory results are obtained

Permission for the patient to resume his usual occupation subsequently depends upon the progress of his recovery and on the occupation Obviously a patient with a sedentary occupation may return to work earlier than one who does manual labor the latter must usually seek a new type of work

Since the pain disappears within a few hours or days after the onset of the attack and the succeeding soreness is equally transient it is often difficult to convince patients that rest in bed is necessary In this instance it is advisable to *explain that a wound in the heart must heal just as a fractured leg* and this takes time Phenobarbital and the new tranquilizers will prevent patients from becoming too restless

Food At the same time the intake of food is restricted The vomiting that occurs on the first day often makes it impossible for the patient to take any food Later tea fruit juices consommé and milk are given Solid food may be added on the third or fourth day if the patient s condition permits it However the patient must be warned against heavy meals even in the future Frequent small feedings represent the method of choice About 1500 to 1800 calories usually suffice for the bedridden patient and care must be taken to have the food easily digestible and appealing to the patient

Bowel Movements It is safe to allow three days to pass without the patient having a bowel movement On the evening of the third day, a mild *cathartic* — milk of magnesia cascara sagrada or mineral oil — may be given if necessary For patients in a serious condition this is much better than an enema Straining and forcing at stool should never be permitted The patient is advised never again to strain in order to evacuate the bowels Against meteorism a rectal tube is inserted and heat is applied to the abdomen

Sexual Intercourse Smoking The former is forbidden for a variable time but at least for four months The exact period will depend upon the condition of the patient Smoking is forbidden but moderate amounts of alcohol are allowed

Insulin In diabetics with coronary sclerosis and anginal pain particularly in those with a recent myocardial infarction the use of insulin should be avoided as long as possible Even a blood sugar of 200 mg per cent need not *constitute* an indication for the administration of insulin Acidosis uncontrolled by diet or preparation of a patient for operation may necessitate its use

While large doses of insulin often do not influence the heart directly and diabetics with coronary sclerosis take insulin without harm for years there are indisputable observations which indicate that even small doses of insulin may aggravate the cardiovascular situation in some individuals and may even occasion anginal attacks This may be explained by the increased secretion of adrenalin causing tachycardia and hypermotility of the heart when the blood sugar falls If insulin is necessary hypoglycemia should be carefully avoided and vasodilators should be administered at the same time

Digitalis A very important and frequently disputed question involves the permissibility of prescribing digitalis to patients recovering from a recent attack of coronary thrombosis It has been argued that digitalis is harmful because it narrows the coronary arteries furthermore it increases the vigor of contractions thus bringing the danger of cardiac rupture or of embolism from mural thrombi In the first acute phase of myocardial infarction rales at the bases of the lungs or a moderate enlargement of the liver are very frequent This alone is not sufficient to indicate digitalis therapy Even if the rales increase and dyspnea with cough appears it is possible in a vast majority of cases to provide subjective relief to prevent the appearance of pulmonary edema and to diminish the rales by small doses of morphine or pantopon (0 01—0 015 Gm) Within a short time as late as eight or ten days the rales usually disappear under the treatment outlined above without resort to digitalis

When cardiac failure progresses despite rest and the administration of morphine digitalis must be given since no other therapy corrects the situation This will be necessary more often when the blood pressure has been high before the occlusion and does not fall appreciably in the attack In patients with a hypertrophic and dilated left ventricle digitalis gives better results than in congestive failure of a patient with a left ventricle which is normal save for a circumscribed necrosis due to myocardial infarction

Not rarely patients who had a myocardial infarction and begin to walk around or start working develop congestive heart failure or attacks of pulmonary edema They respond readily to digitalis which is required for several months Gradually with the consolidation of the myocardial scar the doses of digitalis can be diminished and one day omitted Rarely more than 0 2 gram of digitalis leaves daily are needed

Surgery Elective surgery will be postponed until four months after the attack In general surgery is tolerated well in coronary heart disease with judicious and cautious use of anesthesia (Keys et al)

Air Travel We permit patients who have had a myocardial infarction of average severity and who have fully recovered to fly four months after the attack It is clear that no patient who has congestive heart failure tachycardia or hypotension should be permitted to fly

At levels over 7 000 feet patients with coronary sclerosis should be given oxygen This is the level at which most pressurized airplanes fly

CORONARY STENOSIS AND ANGINA ON EFFORT

Atherosclerotic stenosis of the branches of the coronary arteries or stenosis of the orifices secondary to syphilitic aortitis are responsible for the classical angina on effort so admirably described by Heberden

If an angina on effort begins suddenly the occurrence of an asymptomatic occlusion of a coronary artery should be considered At post mortem in patients with angina on effort at least 1 and often 2 coronary arteries will be found occluded

INCIDENCE

In this condition the history is of paramount importance An advanced stenosis of the coronary orifices or arteries may exist with no abnormal findings Therefore knowledge of the typical subjective complaints is necessary and a detailed history must be obtained The statement so often recorded on charts — patient has anginal pain or pain in the precordial area — does not suffice

The pain is definitely related to effort At first it may occur only on great effort such as climbing several flights of stairs running after a train or walking uphill However sooner or later even walking on level ground induces the distress Commonly the pain is located in a very characteristic manner behind the sternum It may spread to the left or right chest to the left or right side of the neck the shoulder or the arm If severe it may reach the jaw or the ulnar aspect of the left or right hand In unusual cases it spreads downward and then radiates more often to the upper right side than to the left side of the abdomen Sometimes the retrosternal pain is absent and in its place there is only pain in the left elbow or hand or even the jaw Very rarely the distress may extend into the left leg down to the knee

The pain is usually described as a viselike constriction or a choking compressing sensation

Not uncommonly the presence of pain is denied a sensation of choking pressure or burning may exist or the patient may even disclaim these sensations to complain merely of a weakness of one or both arms As in coronary thrombosis painful sensations may be absent despite coronary stenosis and the intensity of pain permits no conclusion with respect either to the extent of the lesion or to the prognosis

The pain may force the patient to stop walking or working If this is done the typical pain subsides in a few minutes If the patient resumes walking the distress may recur but occasionally it does not return even if the walk is prolonged rarely the pain disappears even when the patient does not stop an observation noted by Heberden The patient walks off the pain

This is explained in the same way as the pain experienced by young healthy people at the beginning of strenuous exercise (mountain climbing cycling rowing) The coronary circulation does not adapt itself immediately to the increased demands from exercise and a myocardial hypoxia appears in the first minutes of physical activity With adequate dilatation of the coronary arteries due to reflexes and action of local metabolites an increased blood supply to the myocardium is obtained in the following minutes the pain disappears and the patient gets his 'second wind This mechanism also explains the common phenomenon that walking in the morning elicits the pain quickly while walking much longer distances later in the day fails to elicit unpleasant sensations (first effort pain)

It is also typical for these patients to note no pain when walking in their apartment or building for a long time walking one block in the open air elicits it

Exertional pain appears more often and with greater regularity and in some patients even exclusively if they walk after a meal or if they walk in cold and windy weather After a heavy meal the cardiac output increases almost 50 per cent this higher level is maintained for one to three hours (Grollman) If patients take a postprandial walk the work of the heart is further increased and the demands for blood may become sufficiently large to cause ischemia of the heart muscle if coronary stenosis is present The exercise tolerance of patients with angina pectoris following a meal is reduced on the average 25 per cent (Wayne and Graybiel) Walking against the wind increases work the cardiac output is also increased when cold air is blown on the skin of an experimental animal Cold leads to an increased output of adrenalin

In some cases anginal pain appears at the beginning of a meal and even when the patient swallows In this instance reflexes from the lower esophagus and stomach are obviously responsible as discussed before A similar mechanism may explain attacks appearing at rest and disappearing with the eructation of gas or the passage of flatus Experimental distention of the abdomen by gas also causes a reflex coronary vasoconstriction (Gilbert et al)

Anginal pain also appears on excitement Under these conditions the output of adrenalin may increase the blood pressure and heart rate and precipitate the pain (Paab)

Thus in coronary stenosis any mental or physical strain anything that increases the work of the heart and therefore its need for oxygen causes pain Great apprehension and anxiety (fear of impending death) often accompany the pain The mechanism responsible for this anxiety is unknown

SIGNS

Physical examination discloses no signs characteristic for angina pectoris due to coronary stenosis The physical findings are often normal This was stressed in the discussion of coronary sclerosis and it will be mentioned again in regard to luetic stenosis of the coronary orifices and aortitis Many surveys reveal that approximately 20 per cent of patients with exertional angina yield normal physical findings including x ray and electrocardiograms Therefore reliance must be placed mainly on the history

Many patients however do have abnormal findings An elevated systolic and diastolic blood pressure a dilated aorta an abnormally accentuated second aortic sound a rough systolic apical or aortic murmur caused by an athero sclerotic thickening of the mitral or aortic valves may be present The electro cardiogram may show T wave changes or wide slurred and notched QRS com plexes While these findings may aid in a doubtful case because they show that myocardial involvement is present they do not conclusively prove that a coronary artery stenosis exists and is the cause of anginal pain

The desire to obtain compensation the information obtained from news papers or from friends who suffer from angina pectoris may influence the history on which the physician relies for the diagnosis This coupled with the fact

that pain on effort occasionally occurs in conditions other than coronary stenosis makes understandable the desire to confirm the diagnosis by objective findings

Such confirmation is possible if the electrocardiogram is taken after exertion (Scherf et al)

Exercise Test At rest these patients often have a normal electrocardiogram despite marked coronary stenosis since the blood supply to the heart may still be adequate For the same reason they offer no symptoms or abnormal signs at rest On exertion however the oxygen requirements of the heart muscle increase but a larger blood supply to some areas is impossible owing to the existing stenosis Therefore pain as well as electrocardiographic changes may appear after exertion

Alterations in the electrocardiogram after effort have been known to occur in patients with angina pectoris (Wood and Wolferth) This procedure however was not recommended as a diagnostic test because the clinical observations are more likely to be significant from a diagnostic standpoint than the electrocardiographic phenomena Since the physical findings are often negative and — if present — are by no means typical the study of the electrocardiogram following exercise has been recommended in order to diagnose coronary stenosis (Goldhammer and Scherf)

The changes which appear after exercise in coronary stenosis consist of an abnormal depression of the RS T segment and the disappearance or inversion of the T waves in leads I and II and the precordial leads V 4 6 Great caution must be used not to confuse normal changes which appear in the electrocardiogram after physical exertion with those due to coronary stenosis The error committed most frequently is to declare a physiologic depression of the RS T segment after exercise to be pathologic Thus many normal postexercise electrocardiograms are called abnormal (false positive tests) In order to avoid this one should never interpret a depression of the RS T segment of less than 2 mm as abnormal The T of the P wave is markedly depressed after exercise and because of its long duration it depresses the RS T segment so that the reference point for the evaluation of the position of the RS T segment should be the position of the string at the beginning of the QRS complex and not the zero line The changes described above as pathologic are not observed in healthy subjects after light or even after strenuous exercise Only after unusual strain (e g

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FIG 81 The electrocardiogram of a patient with coronary stenosis caused by athero sclerosis and angina on effort before (a) and after (b c d) exercise

FIG 82 The three standard leads are followed by V 2 and V 5 The tracings were obtained from a 65 year old man with angina on effort due to coronary sclerosis At rest (a) the T waves are low but positive Two minutes after exercise (b) there is a borderline depression of the RS T segments and atrial extrasystoles appear (V 2 and V 5) Six minutes later (c) there is a definite inversion of the T waves which are abnormal fifteen minutes after the exercise (d) the T waves are higher than prior to undertaking the exercise This is a common phenomenon (Scherf and Goldhammer)

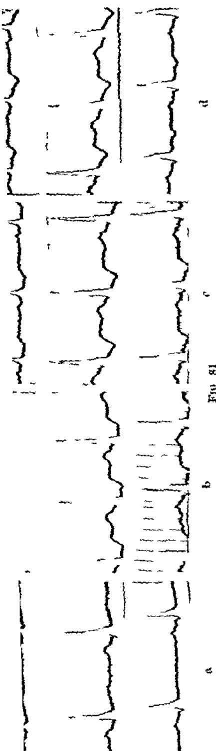


FIG 81

a b c d

FIG 82

marathon running) have similar changes been reported as a rare occurrence in the normal heart Patients without coronary stenosis (myocardial or other types of heart lesions) likewise do not show the changes mentioned They are characteristic of coronary stenosis They have been observed in myocarditis although rarely

The series in figure 81 was obtained from a 56 year old man with coronary stenosis and angina on effort Physical examination gave normal results The first tracing (figure 81a) was taken at rest and shows only low T waves in the three limb leads The second tracing taken immediately after the patient walked up and down two flights of stairs shows depression of the RS T segments and of the T waves (figure 81b) In figure 81c and figure 81d recorded five and ten minutes after the exercise the changes are still very marked although the exercise had stopped

If patients are asked to do no more exercise than they perform repeatedly during their daily occupation this test involves no risk In some cases the exercise test is normal before but positive after a meal The test shows abnormal changes in 80 per cent of patients with coronary stenosis The alterations are independent of the presence of pain and depend solely upon the amount of the coronary blood flow They are sometimes absent if nitroglycerin or theophylline are given immediately before the test is done The changes in the electrocardiogram sometimes persist for 50 minutes after the exercise and therefore are scarcely the result of hypoxia alone (Scherf 1935)

Figure 82a shows the three standard leads as well as the leads V2 and V5 from a 65 year old man with angina on effort The only abnormality consists in low T waves in all leads The electrocardiogram obtained immediately after exercise (figure 82b) shows a depression of the RS T segment which is borderline An inversion of the T waves followed in figure 82c which was registered 6 minutes after the exercise In figure 82d obtained 15 minutes after the exercise the electrocardiogram is again normal Actually the T waves are higher than before the exercise which is a common phenomenon (Scherf)

We are opposed to Master s modification of the test since we do not think that the amount of work performed by the patient should depend upon the age sex and weight The condition of the coronary artery should dictate the amount of work as we originally recommended Work undertaken in accord with Master s tables is too much for one and too little for the second patient This is why work must be done twice or three times (double treble tests) But then we are no longer dealing with a standard test Since a given amount of work will mean a different load for the heart whether the work is done by a person in good or bad physical training before or after a meal slow or fast relaxed or with tension a standard' performance is from the beginning impossible

Anoxemia Test The tests in which hypoxemia is produced by breathing from a bag (Rothschild and Kissin) or by breathing a mixture containing reduced amounts of oxygen (Dietrich and Schwiegk) have the disadvantage of requiring additional apparatus Also they are less useful because abnormal changes are

occasionally seen in healthy subjects in anemia and in other conditions (Larsen) they are not specific for coronary stenosis

Ballistocardiogram Even in patients who do not show any abnormality in the electrocardiogram and who exhibit normal clinical findings the ballisto cardiogram may reveal abnormalities An early M form appears the I wave becomes smaller or the J wave is M shaped The waves are abnormally low and abnormal respiratory changes appear However patients with typical angina pectoris may have a normal ballistocardiogram Probably it is abnormal only in those who have small necroses and fibroses Results must be evaluated with caution Thus one must keep in mind that an abnormal ballistocardiogram is found in only 80 per cent of patients with a healed myocardial infarction

Differential Diagnosis

The differential diagnosis between angina pectoris due to coronary stenosis and the pain of coronary occlusion usually is easy The tables used in older books in order to illustrate this are therefore unnecessary today In coronary stenosis pain typically follows the provocative factors mentioned previously whereas in coronary thrombosis the pain appears without visible cause In coronary stenosis the patient soon learns the relation between certain acts and the pain and tries to avoid precipitating an attack In coronary occlusion the pain usually lasts for hours certainly longer than a few minutes In angina on effort due to coronary stenosis the pain disappears quickly if the patient stops walking or if the reason for the excitement passes One may safely state that whenever the pain lasts longer than five minutes a simple uncomplicated coronary stenosis is no longer responsible The pain in coronary stenosis is regularly relieved by nitrites which do not help in coronary occlusion

The benefit afforded by nitroglycerin in coronary stenosis is so regular that this fact is utilized with great advantage as a therapeutic test Whenever the history is atypical or unreliable it is advisable to administer one tablet of nitroglycerin during the pain If this brings relief within one minute anginal pain is most probably present One must make sure that relief comes within a minute since patients often state that nitroglycerin helped even though further inquiry reveals that five or six minutes were required for the pain to vanish The effect of nitroglycerin is prompt and remarkable even with marked luetic narrowing of the coronary ostia in which instances an increase of blood flow in the coronary arteries due to the drug is impossible It is believed that an increased capillarization the widening of the peripheral sections of the coronary tree helps in these instances An antiadrenergic effect of nitroglycerin has been assumed to exist (Raab and Lepeschkin) The tablets used for this test must be fresh since nitroglycerin deteriorates with time

Apart from the above mentioned characteristics some negative evidence also aids in ruling out coronary occlusion Thus fever leukocytosis and fall of blood pressure are absent in simple coronary stenosis

If patients state that their attacks are increasing in frequency and that the episodes tend to occur more often during rest, that they are becoming more prolonged or that nitrites are less effective, the danger of an occlusion is imminent. As pointed out earlier, in some cases of coronary thrombosis, pain lasting from five to fifteen minutes occurs at rest for a few days before the attack.

In spondylarthritis, in cardiac neurosis and in hiatus hernia, it is occasionally reported that pain occurs on exertion, after meals or excitement, but careful interrogation discloses that there is not always an immediate and direct relation between the alleged releasing factor and the pain; moreover, in neurosis the pain is too brief (stabbing) or too long to permit the diagnosis of coronary stenosis. In spondylarthritis, the pain is often elicited by a certain posture and in hiatus hernia belching brings relief. The latter phenomenon, however, often also appears in true angina due to coronary stenosis.

We have had the opportunity to observe a patient who complained of pain only while lying on his left side. Physical examination gave negative results but the T wave in lead I was low. The patient was put to bed and died suddenly five days later when he turned to his left side on the order of his nurse.

It is particularly important to obtain a very careful history when the examination reveals no abnormal findings. Sometimes, especially at the beginning when an abnormal sensation has appeared but once or twice, a differential diagnosis is difficult or impossible. Some of these patients turn out to have only a harmless spondylarthritis or fibrositis, while others soon develop a coronary thrombosis and may die a few hours after the examination which did not reveal any abnormal findings. Therefore, great caution must be exercised before making a diagnosis as ominous as coronary artery disease or before the patient is dismissed as suffering from a harmless condition.

Decubitus Angina. A small percentage of patients with coronary stenosis have their attacks of angina at rest, particularly at night, for months and years (decubital angina). This type is associated in most instances with a remarkable rise of blood pressure in the attack. The hypertension is often attributed to an exciting dream but usually there is no apparent cause. This type of anginal pain will be discussed at greater length in the chapter on hypertensive crises.

Even if the history of pain is atypical, a positive result of an exercise test or the presence of abnormal findings such as aortitis, hypertension or cardiac enlargement should make the physician strongly suspect coronary disease.

CLINICAL COURSE AND PROGNOSIS

It is extremely difficult to predict the course of the disease and to prognosticate its duration. A patient with a moderate exertional angina due to coronary sclerosis may show no further change for many years. One of us saw a patient with an angina on effort in whom the attacks were unchanged over a period of 24 years. The process may be arrested at any stage. Luetic stenosis of the coronary ostia has a poorer prognosis, since progression is typical for this lesion.

In these patients as in all other coronary artery diseases sudden death may occur at any time While patients with many attacks on the least provocation are in greater danger than those who develop distress only after severe strain such as climbing stairs after a heavy meal accidents happen in both groups

Attacks of angina pectoris may disappear This happens if a narrowed coronary artery becomes occluded by an acute thrombosis or if a slow fibrotic occlusion occurs without the acute signs a of myocardial infarction If the other main coronary vessels are patent and the blood supply to the heart is sufficient on exertion as well as at rest the patient may feel perfectly well for years Anginal pain often disappears with the onset of fibrillation or congestive heart failure In our experience this occurs particularly in groups of patients with angina on effort as a consequence of syphilitic coronary stenosis when the liver enlarges or edema appears if digitalis successfully controls these symptoms the angina recurs although there is no change in physical activity during the interim This phenomenon has not been satisfactorily explained although it has been known to clinicians for a long time

The intensity of the pain on effort has no prognostic significance the electrocardiogram may show marked hypoxia of the heart muscle without much pain in the attack or the pain may be severe while the electrocardiogram shows only trifling changes

Obviously the patient should always be encouraged as to the outlook however in discussing the situation with relatives the physician should not neglect to mention the possibility of accidents that may occur at any time

Therapy

General Management It is vitally important in the treatment of angina due to coronary stenosis to reassure the patient The term angina pectoris should not be used in his presence Nowadays every patient knows the ominous significance of this diagnosis If the pain is explained as a vascular spasm or a disturbance of the cardiac arteries which prevents a normal blood supply to the heart the patient accepts this with much less alarm than the diagnosis of angina pectoris

The patient must avoid as far as possible all factors that tend to precipitate an attack He must avoid great exertion such as is inevitable in climbing stairs or hills Often walking on the level produces no pain whereas walking up a very slight incline immediately releases it An attempt must be made to avoid undue excitement and the patient should have frequent but small meals Protection against cold is important and it is wise to avoid walking against the wind If these rules are observed by a simple alteration of the mode of living and without other therapy one occasionally succeeds in rendering the patient free from attacks

Treatment of Coronary Artery Disease Unfortunately very little can be done to influence the underlying basic illness in angina on effort syphilitic

aortitis or atherosclerosis In aortitis leading to coronary stenosis and angina on effort specific therapy will be of little avail The disease is however less common in recent years It will be discussed in a later chapter

In atherosclerosis all measures hitherto recommended are of dubious value Choline seemed to help in experimental atherosclerosis but this was not confirmed the same holds for methionine and inositol There is no sound basis for the use of these compounds The effect of the commercially available capsules containing unsaturated fatty acids with nicotinic acid and pyridoxin is still under investigation While experimentally the estrogens reduce the degree of atherosclerosis in chicks there is no justification as yet for the therapeutic use of these substances in man because of the side effects

Heparin was found to clear the lipemic plasma and it was recommended to treat coronary atherosclerosis by injections of 50—100 mg of heparin once or twice weekly Fantastic results have been reported but not confirmed

Usually weight loss should be advised Following a marked loss of weight *a significant decrease of serum Sf 12—20 lipids was observed (Walker et al)* A fat poor and cholesterol poor diet is recommended No cream soups glandular organs tongue fish roe cake fried food cream or butter are permitted Cheese may be eaten only if made from skimmed milk At the most two eggs per week are permitted No nuts or avocados are allowed Not more than 25 grams of fat and 75 mg of cholesterol should be ingested per diem While thyroid hormone diminishes the cholesterol content of the blood rarely can it be given to these patients for reasons that are obvious

Bed Rest There is no rationale for continuous rest in bed Often we see patients who were advised to go to bed for four weeks or more because of their angina on effort When they get up the old complaints are present as before The tolerance to exercise is not increased by bed rest When patients live under great strain separation from the sources of anxiety will help

Nitroglycerin The best remedy in an attack is nitroglycerin It is far better than amyl nitrite which has been prescribed since Sir Lauder Brunton s recommendation Not only does amyl nitrite cause a disagreeable odor in the room but the marked cardiac acceleration and the decided fall of blood pressure induced by it are disadvantageous The tachycardia may increase the oxygen requirements of the heart without the possibility of providing an adequate supply so that more pain and marked electrocardiographic alterations result

One starts with the smallest available dose of nitroglycerin usually *1/200 gr* in the form of the easily soluble hypodermic tablets The pharmacist must provide the patient with a fresh preparation which should be stored in a glass bottle or vial it deteriorates readily and loses strength if exposed to air

If the administration is associated with pronounced untoward *symptoms* such as flushes dizziness headache and the like the patient may take half a tablet In this way the dosage is more easily adapted to the needs of the patient In rare cases sweating syncope and other symptoms are provoked by a sudden drop of blood pressure following the administration of one tablet of nitroglycerin

It is therefore advisable to have the patient take his first tablet while at home in bed in order to familiarize himself with its action In very rare cases nitroglycerin aggravates the pain

Some patients are afraid to take nitroglycerin freely This fear is based partly on a misconception arising from the name of the compound and partly because it helps so much that patients are afraid its effect will wear off and will not be available when needed It is well to point out that the untoward reactions disappear if the remedy is used more often while the therapeutic effect remains Moreover there is no danger of a diminished response for the average case if the remedy is taken often It should *always* be within reach of the patient and be taken whenever needed Even if the patient is in doubt whether a particular pain is due to his heart or is of different origin a tablet should be taken Not rarely physicians advise the patient to take tablets only when the pain is severe this is positively incorrect It is better to take 10 tablets too many than one too few Tablets of nitroglycerin need not be put under the tongue keeping them in the mouth will suffice to obtain a satisfactory effect

Of great importance is the prophylactic use of nitroglycerin which was recommended by Murrell and subsequently by others If ascending an unavoidable flight of stairs or walking up a sloping street regularly induces pain the patient should prevent an attack by taking a tablet of nitroglycerin about a minute before the pain is expected In a similar way nitroglycerin should be taken for preventive purposes before business meetings conferences sexual intercourse etc in order to avoid the anginal pain caused by excitement This advice may make most patients cooperate and may free them from distress despite a continuation of their activity Concerning this prophylactic treatment with nitroglycerin it should be remembered that the prophylactic action rarely lasts longer than 10 minutes

Treatment with nitroglycerin in small doses (1/200 gr) given every two to four hours may help patients with many attacks of angina pectoris at rest

We are very satisfied with the slowly absorbable nitroglycerin preparations (Nitroglyn gr 1/10 or 1/25 1 tablet every 12 hours) In some patients headache appears and they are told to take 3/4 or 1/2 a tablet morning and night In more than 60 per cent of the patients much less nitroglycerin is necessary while these tablets are taken since less pain is experienced In order to avoid tolerance this medication is interrupted for one week every 4 or 5 weeks

Other Vasodilators The value of other drugs in angina pectoris due to coronary stenosis is a disputed issue Empirically and on the basis of animal experiments several drugs have been advised for dilating the coronary vascular tree as much as possible thereby enhancing the formation of a collateral circulation

There have been a few series of carefully controlled investigations on ambulatory patients who suffered from angina on effort These patients received different drugs recommended for this condition as well as a placebo The same percentage of improvement was found in those taking the various drugs as

in those who were treated with a placebo (Evans and Hoyle) This result is the basis for the great pessimism that prevails with respect to the possibility of influencing the course of the disease or the condition of the patient by means of vasodilators many physicians stopped prescribing anything but nitroglycerin to patients with angina on effort

We are personally convinced that treatment with coronary vasodilators is useful We have often seen patients ask for a certain prescription because they felt better as long as it was taken It is equally true that certain patients fail to respond to all forms of therapy for the process in the coronary arteries is *too* advanced Nevertheless every patient deserves the benefit of a trial

It is often stated that vasodilators cannot help in cases with advanced coronary sclerosis because the arteries are too profoundly altered The following observation argues against this point At autopsy we repeatedly found the orifices of both coronary arteries almost completely occluded by a syphilitic process although the coronary arteries themselves could not admit a larger amount of blood nevertheless nitroglycerin aided greatly during the anginal attacks of the patient The dilatation of the extracardiac and *intracardiac* anastomoses of the coronary system or an unknown specific action of nitroglycerin (Raab and Lepeschkin) may cause this improvement One may therefore assume that the vasodilators help even in extreme coronary narrowing

Among the compounds related to nitroglycerin erythrol tetranitrate is the best for prolonged and regular administration Its chief drawback is the headache which often occurs even if small tablets (0 005 Gm) are taken three times a day Accordingly not more than 0 003 Gm should be given as a single dose *The advantage of erythrol tetranitrate consists in its more prolonged* action perhaps the result of slower absorption

Headaches also follow the administration of mannitol hexanitrate in a dose of 0 06 Gm three times daily We have not observed any improvment *from* penta erythrol tetranitrate (Peritrate) and dioxelene phosphate (Papaveril phosphate)

Purine bodies such as theobromine sodium salicylate (Diuretin) pure theobromine theobromine calcium salicylate (theocalcin) and particularly theophylline have been used as coronary dilators for many years A stimulating effect on cardiac contraction is combined with definite coronary dilatation Pure theophylline often irritates the stomach and produces nausea In combina*tion with ethylenediamine which acts as a solvent* theophylline is tolerated better the new drug is called aminophylline (euphyllin metaphyllin) and is given in tablets of 0 2 Gm three times a day The enteric coated tablets are tolerated much better but their absorption is slower *Our experience* with the latter type of tablet is much more satisfactory than with plain tablets

A preferable method of administering aminophylline because of more pronounced effect is by rectal suppositories We give 0 5 Gm of the *product* in each suppository and advise the patient to insert one or two suppositories daily Sometimes the administration of 0 5 Gm of theophylline ethlendiamine

(aminophylline) in 30 ml of water as a retention enema is more rapid and more complete Rarely intolerance to the drug is encountered This is manifested by excitement irritability headache or local rectal irritation These events are exceptional as a rule the remedy is well tolerated

Strongest vasodilatation is accomplished by the intravenous use of theophylline The injection of theophylline ethylenediamine must be done very slowly to avoid marked vasodilatation with vertigo and fall of blood pressure The injection should take at least five minutes and it may be repeated daily in the same amount

If an intravenous injection comes under consideration we prefer the soluble theophylline sodium acetate This salt is tolerated much better and does not cause untoward reactions Usually a 5 per cent solution is employed and 5 ml are given as the first dose This amount may be increased by 1 ml daily until the full dose of 10 ml (0 5 Gm of theophylline sodium acetate) is given with each injection In a very small fraction of the cases a sensation of irritability and excitement may limit the physician to giving no more than 5—6 ml daily A total of 12 to 15 injections constitutes a series With these injections more is accomplished than with any other therapeutic procedure as the coronary dilating effect is pronounced unfortunately improvement often lasts only for the period of administration of the drug

It has been possible to show the therapeutic value of theophylline objectively the electrocardiographic alterations appearing regularly after exertion fail to develop if the same exercise is repeated shortly after an intravenous injection of the drug (Scherf)

The administration of papaverine hydrochloride 0 05 Gm by mouth or 0 02—0 04 Gm intravenously has often been recommended There is no doubt that papaverine is a powerful coronary vasodilator and it should be used more frequently but its price is often prohibitive and in our experience theophylline injections have a better and a more prolonged effect

Atropine has been frequently mentioned as a useful drug for angina pectoris and formerly was often prescribed Since the vagus acts as a constrictor of the coronary arteries and the tonic innervation permits a maximal coronary blood flow only after atropinization some result should be expected On the other hand the amount of atropine permissible is one which does not appreciably affect the heart rate

Since large and effective quantities of all these remedies cannot be given over a long period it seems best to proceed in a manner that allows a combination of several agents having partly different points of action Although this combination recalls the polypharmacy of former times results are obtained with this combination that are not approximated by the use of single ingredient We cannot understand why the administration of these drugs in a mixture made in the pharmacy should do harm while the simultaneous ingestion of the same ingredients from different bottles should be useful

The prescription is as follows

	Gm
Erythrol tetranitrate	0 003
Papaverine hydrochloride	0 05
Phenobarbital	0 01
Atropine sulfate	0 0002
Quinidine sulfate	0 1
Acetphenetidin	0 1
Theobromine pure	0 15—0 20

The relatively small dose of erythrol tetranitrate does not cause headache phenobarbital is a central sedative and acetphenetidin advocated already by Huchard is an analgesic In the dose prescribed atropine accomplishes no more than a reduction of vagal tonus Quinidine is a powerful vasodilator and a depressant of the tonus of the autonomic nerves

From this mixture one capsule is prepared such capsules are given three times a day one after each meal Rarely hypersensitivity to phenobarbital quinidine or theobromine is encountered and these drugs must then be omitted from the mixture The capsules are given for 3 to 4 weeks and in many cases there is a definite improvement with regard to the severity frequency and duration of the attacks Naturally refractory cases are encountered since all therapy is ineffective when alterations are advanced Occasionally the symptoms recur if the capsule is stopped under these circumstances there is no objection to another course of administration

The occurrence of spontaneous improvement in patients with coronary stenosis compels one to exercise caution in the appraisal of all therapeutic measures With the capsules just mentioned with nitroglyn with aminophylline suppositories and with intravenous injections of theophylline we possess a powerful therapeutic armamentarium to improve the patient s condition and we have a real basis for hope and encouragement although we cannot alter the course of the disease or influence the dubious outcome

Administration of pressor amines should be avoided Parenteral therapy with Priscoline and Pitressin may lead to severe attacks of angina pectoris

Khellin Promising results have been obtained with khellin preparations obtained from ammi visnaga a wild plant from the Eastern Mediterranean Used widely in Egypt for the treatment of kidney stones and bronchial asthma it has a coronary vasodilating effect that surpasses that of papaverine and aminophylline as was demonstrated by Anrep and his co workers In those patients who tolerate the drug good effects may be obtained we do not agree with those who claim that khellin is of doubtful value In several of our patients the complaints recurred a few days after the drug was withdrawn The dosage is different with different preparations on the market One gives advisedly the smallest dose of a preparation which is on the market once daily and gradually increases the number of tablets to as many as are tolerated Unfortunately side effects

such as severe nausea, vomiting, diarrhea, excitation or abnormal sedation, weakness, confusion, depression and fever appear in about 60 per cent of those who take the drug.

Propylthiouracil. Radioactive Iodine. Surgical thyroidectomy is now abandoned in favor of the chemical blocking of the formation of thyroid hormone with propylthiouracil or similar compounds, or with radioactive iodine. This therapy, *sponsored mostly by Raab and Blumgart, brings a slow improvement* since all thyroxin already formed by the gland must be first exhausted, a process which may require weeks. Patients with angina pectoris seem to do best with a basal metabolic rate of minus 15—20 per cent. Clinical observation is a better guide. *One administers 20—100 millicuries of radioactive iodine in three divided* doses. Against the objection of a possibility of enhancement of atherosclerosis by the myxedematous state, Blumgart has emphasized that in a very limited number of subjects who were examined at necropsy years after thyroidectomy, *no evidence of advanced coronary sclerosis was observed.*

Tobacco. Smoking should be discontinued. Although there is no proof that smoking alone causes coronary sclerosis, it is equally indisputable that the angina pectoris of coronary stenosis may be aggravated by smoking. It is a *common observation* that *heavy smoking in healthy youngsters causes precordial* pain which gradually disappears if the smoking is discontinued. Tobacco angina is, however, rare. In patients with and without organic heart disease temporary changes in the electrocardiogram *have been observed following smoking of a single cigarette.* Patients with angina pectoris *may improve when* they stop smoking. Whether the detrimental effect of smoking is due to vaso-constriction or the increase of heart rate and blood pressure is not decided.

In young men, angina pectoris *seems to occur* more often among heavy smokers than non-smokers. In elderly people, no differences were observed in the incidence between both groups.

Methonium. We lack experience in the therapy of angina pectoris in hypertensives with methonium. *Doyle and Kilpatrick treated 50 patients. As to be* expected, spontaneous pains appeared in some and the treatment had to be terminated. Many patients, however, showed improvement and in one third anginal pain disappeared. We saw improvement with rauwolfia.

Alcohol. The moderate use of alcohol is permissible; indeed, it had been regarded as a beneficial agent owing to its vasodilating effect and was recommended by Heberden. There is no proof that alcohol dilates the coronary arteries. Beer and champagne, like other carbonated drinks, should be avoided because of the resulting elevation of the diaphragm, which is not well tolerated.

Spa Treatment. Spending a few weeks at a health resort has the advantage of rest and relaxation, but it has the disadvantage that the patient may learn *too much about the symptoms and complications of his disease from fellow* patients. Naturally, it is beneficial to spend the winter in a southern climate; however, while this adds to the well being of the patient, he should be informed that this will not cure his condition.

Irradiation of Adrenals Starting from the theory that attacks of angina pectoris in cases of coronary stenosis occur after physical exertion exposure to cold weather or emotional factors – conditions in which according to Cannon large amounts of adrenalin are discharged from the adrenal medulla – irradiation of the adrenals with roentgen rays has been recommended (Raab) Six single treatments are given on consecutive days Three treatments are applied to the left side and three to the right each side being treated on alternate days Two hundred roentgen units are given at each treatment The size of the field is 15 × 15 cm 200 kv 20 ma 50 cm target skin distances 1 5 mm Cu plus 1 0 mm Al filter

In more than 20 personally observed cases the results were satisfactory and seemed to go definitely beyond the individual variations in the course of the disease and psychic effects inherent in any therapeutic procedure

Surgery When the attacks cannot be controlled medically and occur with such frequency that life is intolerable to the patient surgical measures may bring relief Some patients suffer such agony that they are willing to undergo any surgical intervention which promises help

Candidates for any surgical procedure must be carefully selected and one fact should be constantly kept in mind namely that spontaneous improvement may occur at any time irrespective of the intensity of subjective sensations or objective findings The surgical procedures may be divided into three groups

(1) Operations aimed at interrupting pain fibers on their way to the centers This is a purely symptomatic measure without influence on the pathologic process

(2) Thyroidectomy which does not influence coronary blood supply directly

(3) Operative procedures designed to increase the blood supply to the heart by creating anastomoses

INTERRUPTION OF PAIN FIBERS Since Francois Franck s demonstration that sensory fibers from the heart pass over the sympathetics operations on the cervical and dorsal sympathetics have been recommended Many of the original procedures proved useless or were not compatible with anatomic facts The mortality was over 10 per cent Extirpation of the stellate ganglion afforded relief in a fair number of cases although sensory fibers also run from the heart directly to the upper thoracic ganglia Extirpation of these ganglia bilaterally and section of the upper five dorsal roots are very formidable operations No improvement is obtained in 8 per cent of the patients Intercostal neuralgia appears in 10 per cent Pleural effusion radiculitis and even transverse myelitis have been reported Therefore paravertebral anesthesia with a mixture of novocaine and alcohol is preferred at present When done by a competent physician the risk of complications is small and the percentage of patients benefited is great However in over 50 per cent neuritic complaints result which may be very troublesome Relief from the angina may last for a month or it may be permanent Instead of pain patients receive other warning signals such as sensations in the jaw behind the sternum or choking

TOTAL THYROIDECTOMY This has been abandoned since the advent of the thiourea drugs and radioactive iodine which were discussed above

OPERATIONS FOR INCREASING THE BLOOD SUPPLY TO THE HEART Opinions about the value of operations intended to increase the blood supply of the heart by creating anastomoses with the extracardiac circulation are divided A definite indication for such an operation would be the progressive narrowing of the coronary ostia by syphilis This condition can be diagnosed clinically and since all other therapeutic procedures are useless an operation may be justified once the diagnosis is established In patients with coronary sclerosis we hesitate to advise surgery When attacks increase in intensity and occur more frequently even at rest often a coronary occlusion threatens Therefore the mortality of these operations is so high signs of a myocardial infarction appear often during surgery or immediately afterward

Among the operations reported there are several which have become well known Grafting a part of the left pectoralis muscle on the heart grafting omentum on the exposed heart (cardio omentopexy) and the creation of pericardial adhesions by talcum powder (cardiopericardiopexy) (Thompson) or by bone dust (Beck) represent the chief methods recommended Vein grafts between the systemic arteries and the coronary sinus veins were performed (Beck et al) Creation of this type of arteriovenous fistula is attended by a high mortality The De epicardialization operation with a 95 per cent phenol solution (Harken et al) seems promising No proof has been given that following a surgically induced pericarditis sufficient anastomoses form between pericardial and coronary vessels

Even implantation of mammary arteries into the left ventricular myocardium (Vineberg) occlusion of the coronary sinus vein and pericoronary neurectomy (Fauteux) have been recommended There is as yet too little experience available to evaluate the effect of the ligation of both mammary arteries in the second intercostal space

CORONARY INSUFFICIENCY (CORONARY FAILURE THE INTERMEDIATE SYNDROME) AND LITTLE INFARCTIONS

The fact that the currently fashionable diagnosis of coronary insufficiency indicates only a physiologic state and not a clinical entity has been stressed in the introduction to this chapter The term is widely used to indicate a great variety of conditions Danielopolu employed it early to indicate the occurrence of angina pectoris without coronary disease during strenuous exercise Physiologists then used it to describe a blood supply to the heart which does not fulfill the need i e the oxygen requirements Some of them spoke rather vaguely of a coronary insufficiency when there was an anemia or carbon monoxide intoxication Under these circumstances the coronary arteries are normal but the supply of oxygen to the heart alone suffers Great confusion was created subsequently Katz describes coronary thrombosis with myocardial infarction

under the heading of coronary insufficiency Master described necrosis or infarction of the heart muscle without complete occlusion of a coronary artery as coronary insufficiency and later interpreted this term to mean attacks of pain in between angina pectoris and myocardial infarction without or with very little fall of blood pressure elevation of the sedimentation rate and no QPS changes in the electrocardiogram Shock is rare Nitroglycerin helps little or not at all A similar syndrome was described by Freedberg et al as coronary failure and by Graybiel as the intermediate syndrome

In our opinion most of these patients have sustained *little infarctions* an extremely common but little recognized condition

A very odd situation prevails at the present time large classical infarctions are readily diagnosed while little infarctions (like the little strokes emphasized by Alvarez) are not recognized We have seen such infarctions occur repeatedly in some individuals over a period of years Contrary to the statements of some authors these little infarctions like the (larger) rudimentary infarctions of Holzmann may be accompanied by extremely severe pain which lasts for hours There may be a very slight rise of temperature but usually there is none at all The blood pressure remains unchanged or falls a little and only temporarily the sedimentation rate rarely becomes abnormal very often the electrocardiogram is normal since the lesion is intramural not reaching the subepicardial or subendocardial layers occasionally it shows flattening or a transient inversion of the T waves in some leads for the most part the V leads of the chest The tracings described by East and Oram belong here

The attacks are rarely caused by thrombosis of a coronary vessel Usually a fibrotic occlusion of a small tertiary branch is responsible (Wolkoff) The fibrotic occlusion of tertiary branches of the coronary arteries caused by coronary sclerosis is particularly common in hypertension It will not of course be prevented by the administration of anticoagulants It is in our opinion a frequent cause of little infarctions

The patient may have only one such attack if all findings are normal or if he remains healthy over a period of years the diagnosis of coronary disease is often not made In other patients such attacks occur almost daily for weeks or months and require repeated injections of morphine In some cases a series of such attacks leads to myocardial fibrosis without a large area of necrosis but causing heart failure There are countless variations of the clinical picture At any time the attacks may subside A large infarction may appear after years of well being

Such patients require rest only for a few days They may have bathroom privileges Treatment is symptomatic

In our opinion the diagnosis of coronary insufficiency coronary failure or intermediate syndrome (Graybiel) is less exact in these cases than the recognition that we are dealing with little infarctions caused by occlusion of small branches of the coronary arteries

The term "coronary insufficiency" is justified only with a qualification indicating a particular pathophysiologic state, such as coronary insufficiency due to coronary stenosis (syphilitic) or paroxysmal tachycardia, aortic stenosis, acute hemorrhage and so forth. We prefer, however, to speak of a myocardial hypoxia in these conditions — thus indicating the etiologic mechanism — rather than a coronary insufficiency.

ANGINA PECTORIS DUE TO AORTIC AND MITRAL VALVE LESIONS

Anginal and precordial pain is not rare in rheumatic mitral lesions and in rheumatic or syphilitic aortic valve lesions. Such cases frequently are appraised incorrectly because the radiation of the pain, its constant appearance, duration and occurrence at rest are atypical.

Mitral Stenosis. The association of this type of pain with mitral valve lesions, especially when stenosis is preponderant, has been known for a long time and different theories have been advanced to explain the relationship (p. 197). Exertional pain is uncommon in this lesion since dyspnea prevents great exertion, and difficult breathing together with palpitation dominate the picture. If anginal pain appears at rest, the electrocardiogram taken during the pain shows evidence of myocardial ischemia (Scherf and Goldhammer). Therefore, an insufficient blood supply to the heart must be assumed. This might be caused by higher intraventricular pressure in the right ventricle, which increases resistance in the peripheral coronary vascular tree. The appearance of anginal pain in cor pulmonale (see later) makes it probable that some of these pains originate in the pulmonary artery when the pulmonary arterial pressure is increased. In favor of this assumption is the fact that successful mitral surgery causes this most annoying symptom to disappear.

Aortic Stenosis. In aortic stenosis a similar mechanism seems active to some extent in the left ventricle. This lesion is associated with anginal pain more often than are mitral lesions because the patients are able to perform physical work without dyspnea even when the aortic stenosis is rather advanced. In this lesion pain is also common during complete rest. The electrocardiogram in these cases, if taken during an attack of pain, repeatedly shows the same alterations as in coronary stenosis (Scherf, 1935). A suction effect exerted on the coronary ostia has also been held partly responsible for the causation of the pain. It is more probable that the unusual hypertrophy of the left ventricle encountered in this lesion and the increased intraventricular systolic pressure lead to myocardial hypoxia.

Sometimes in aortic stenosis pain recurs so frequently that the patient is unable to take more than a few steps without pain or is awakened nightly from sleep. Since there is no dyspnea, pain is the only complaint, although this pain is so distressing that the morale of patients is shattered and they may contemplate suicide.

Aortic Insufficiency In the presence of a syphilitic aortic insufficiency anginal pain is often due to a stenosis of the coronary ostia in the course of the aortitis Anginal pain occurs however in all types of aortic regurgitation without coronary involvement

The combination of aortic insufficiency and angina pectoris has been known for almost a century In some cases of aortic insufficiency of rheumatic or syphilitic origin the anginal pain is unusually severe although the coronary arteries are normal this is not rare in children and young adults or in older patients This anginal pain was found to occur in 8 per cent of patients presenting aortic insufficiency (Laplace) The pain has been explained by the low diastolic blood pressure (White and Mudd) an explanation which seemed logical when the coronary blood supply was believed to depend exclusively on the height of the blood pressure the fact that the attacks occurred mostly at night was explained by the particularly low blood pressure levels existing at that time On the other hand patients with aortic insufficiency and very low diastolic blood pressure have no more attacks than those with somewhat higher pressures (Laplace) Furthermore it is easy to find that the blood pressure values during the attack are far from low In our opinion patients with aortic insufficiency and angina pectoris in the absence of a syphilitic stenosis of the coronary ostia belong to a group discussed in the next section — patients with hypertensive crises In the same group may be placed some patients with aortic stenosis and anginal pain

Treatment Nitroglycerin invariably gives relief from the anginal pain in all these patients with mitral and aortic lesions Our measures for preventing the recurrence of attacks are limited We have noted beneficial effects from theophylline given intravenously This alone may procure a restful night without anginal pain particularly when the injection is given in the evening The relief is only temporary however and recurrences tend to follow the discontinuance of injections In some cases rectal suppositories of aminophylline in a dose of 0 5 Gm help if they are inserted in the evening The oral administration of aminophylline is useless

These patients are often willing to undertake any treatment suggested by physicians to obtain relief surgical intervention may be indicated One of our patients secured immediate and lasting relief by total thyroidectomy Chemical thyroidectomy with thiouracil is of great help (Scherf and Terranova) Further therapeutic measures will be discussed in the following section

ANGINA PECTORIS IN HYPERTENSIVE CRISES

Since the classical description by Pal paroxysmal and transient rise of blood pressure is called a hypertensive crisis Such crises occur in a variety of conditions Pal described them in acute nephritis in the toxemias of pregnancy uremia and in lead poisoning We shall limit the description of hypertensive crises to the types encountered in cardiovascular disorders We are dealing

with a rather well known clinical syndrome which is often associated with angina pectoris Hypertensive crisis associated with pheochromocytoma will be discussed in the section on hypertension

Hypertensive Crises in the Absence of Pheochromocytoma

For many years it has been known that the blood pressure rises during an attack of angina pectoris This increase is so regular that Pal called angina pectoris an angiospastic crisis In more than 100 cases the blood pressure was regularly taken by one of us during an attack of anginal pain appearing at rest and the rise of blood pressure (which involved both the systolic and diastolic pressures) was never missed in decubital angina with the exception of certain special cases (attacks due to paroxysmal tachycardia pulmonary embolism etc)

Incidence Attacks of paroxysmal hypertension with anginal pain are very common in patients with aortic insufficiency at any age including childhood The same syndrome occurs in aortic stenosis aortitis moderate hypertension coronary sclerosis and occasionally in women with climacteric symptoms

Symptoms and Signs The symptoms closely approximate those observed in patients with a pheochromocytoma The patients suddenly and unexpectedly develop palpitation with some oppression which often develops into agonizing retrosternal pain with the typical radiations noted in angina pectoris There is profuse perspiration and the initial pallor is followed by a strong facial flush The systolic pressure often rises more than 100 per cent and values over 300 mm Hg are frequently recorded during the attack even when the systolic blood pressure does not exceed 130 mm Hg in the interval The diastolic blood pressure also rises but rarely more than 20—40 mm Hg Sometimes the anginal pain is absent and an unusually severe headache is present

A 14 year old boy had a slight insufficiency of the aortic valve after rheumatic fever He developed severe headache for many weeks and the distress recurred every afternoon at about five o clock The blood pressure values were always found around 110/40 except during the attack when they rose to 220/70 The episodes disappeared suddenly without treatment and did not recur (Scherf 1935) There was no decompensation A similar severe headache with paroxysmal hypertension and no anginal pain was observed by one of us in a patient with coarctation of the aorta

The attacks may last for a few minutes or several hours Very often they recur nocturnally and then with extreme punctuality at exactly the same hour They may also be diurnal In some cases as in pheochromocytoma it is possible to reproduce an attack by having the patient immerse the hands in cold water or by mental or physical strain In most cases the attacks come and go without apparent reason The attacks disappear during a febrile episode

Whereas the attacks associated with pheochromocytoma usually occur with increasing frequency severity and duration unless the tumor is removed the attacks reported in this section may disappear at any time and may never recur In several patients with this syndrome who succumbed we searched

very carefully for evidence of the chromaffin tissue or the presence of a chromaffin cell tumor but without success

Hyperadrenalinemia and hyperglycemia have been found during a crisis of this kind (Bernal Kugelmann) but this is not significant since every stimulation of the sympathetic system is accompanied by an increased outpouring of adrenalin like substances into the blood

That these attacks are not due to an increased output of adrenalin alone is shown by the observation that in some of these patients a local vascular spasm appears during the attack In two of our patients marked pallor of the left arm appeared simultaneously with an increase of blood pressure and anginal pain

These local crises may involve the meningeal vessels causing the headache or the cerebral vessels may be affected causing transient paralysis (cerebral crisis) in rare cases local arterial retinal spasm (retinal crisis) was observed *causing amaurosis (Pal)*

In acute and chronic nephritis and in the malignant phase of hypertension similar general and cerebral vascular crises occur causing increased blood pressure headache vomiting tonic and clonic convulsions coma temporary paralysis and even transient amaurosis Local vascular spasm is responsible

Very rare are depressor crises during which entirely without premonition and without visible cause a considerable fall of blood pressure occurs with weakness general sweating and nausea These attacks last for minutes or hours Their mechanism is unknown Careful observation fails to detect evidence of coronary thrombosis One of our patients with coronary sclerosis who survived two attacks of this type succumbed during a third more than two years after the second

The hypertensive crises are often unrecognized because in the interim examination yields negative results even if a slight aortic insufficiency is found in a young boy or girl the examining physician who does not see the patient in an attack fails to consider the possibility that a quite different syndrome is present when complaints occur Women after the menopause who do not show any abnormality when examined between attacks are considered to be neurotics All gradations between very severe pain and moderate retrosternal pressure are observed Frequently the symptoms are disregarded or considered nervous and sedatives are prescribed

Mechanism The developmental mechanism of this pain is not clear Equally obscure is the problem of why the crisis occurs so often in connection with aortic insufficiency and why only a few patients with this lesion present it Most of the patients originally observed by Pal had an aortic insufficiency and since some of them also suffered from tabetic crises the application of the term *crisis* for a paroxysmal rise of blood pressure seemed indicated

Examination of the blood pressure during an attack makes it clear that the anginal pain develops when the pressure level reaches a certain point Lewis speaks of a vasomotor storm in the splanchnic sympathetic system the cause

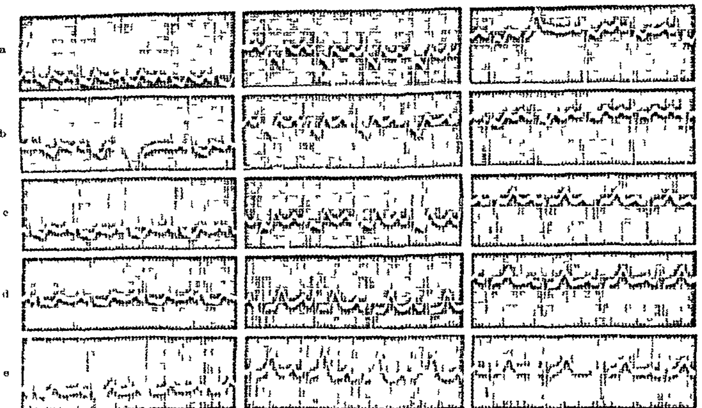


Fig 83 A series of electrocardiograms obtained during a hypertensive crisis with anginal pain

of the abnormal sympathetic vasoconstrictor impulses the reason why they appear and vanish is unknown

If a patient with syphilitic or atherosclerotic coronary stenosis develops this paroxysmal hypertension the occurrence of pain is understandable The sudden rise of blood pressure and the higher heart rate usually associated with it increase the demand for blood if due to coronary disease an adequate supply is not forthcoming pain will result If an electrocardiogram is registered in such a patient during a hypertensive crisis and compared to the electrocardiogram obtained during the anginal pain after physical exertion the two are seen to be exactly the same (Hausner and Scherf) this was noted in 47 cases

Figure 83 was obtained from a 39 year old woman with syphilitic aortitis *narrowing of the orifices of both coronary ostia was found at necropsy* The patient had angina on effort and severe attacks of angina pectoris at rest with good response to nitroglycerin During the attacks appearing at rest the blood pressure rose considerably

The electrocardiogram showed only left axis deviation On exertion marked changes appeared in the T waves The same changes developed during attacks of angina pectoris occurring at rest

The tracing in figure 83a was taken during an attack of severe anginal pain It shows a sinus tachycardia a single ventricular extrasystole in lead III and deeply inverted T waves in each lead The same changes were visible in figure 83b which was registered five minutes later The pain had disappeared in the meantime following the administration of nitroglycerin Figure 83c and figure 83d taken 10 and 15 minutes after figure 83a show gradual improvement The last tracing (figure 83e) obtained 20 minutes after the first one shows almost complete recovery There is still a slight depression of the RS T segment in lead I

These tracings prove the existence of a marked hypoxia of the heart muscle during these attacks persisting even after the pain had disappeared

Patients with an aortic insufficiency may suffer from severe attacks of angina pectoris but the *coronary arteries are found normal at necropsy* (Lewis) In one case of this kind among our observations the coronary arteries were normal at necropsy but the electrocardiograms recorded during the attacks were always markedly altered and showed evidence of hypoxia of the heart muscle

One must therefore assume that the pain in these patients probably results from a participation of the coronary arteries with the same narrowing which involves the splanchnic vessels whereby the blood supply to the myocardium becomes insufficient Paroxysmal hypertension also was said to cause narrowing of the coronary arterial tree via the carotid sinus reflexes (Stella) Bilateral denervation of the carotid sinus in two patients with hypertensive crises *however* failed to alter the clinical picture (Scherf 1937)

Therapy Amyl nitrite and nitroglycerin relieve the anginal pain and the headache but the relief is transient within a few minutes the pain recurs The blood pressure may remain high The amount of nitroglycerin which some of these patients take in a twenty four hour period is sometimes staggering As

early as 1905 Pal noted success from only one agent sodium thiocyanate Papaverine also recommended by this author in our experience is rarely of help

When the attacks recur too often and patients are incapacitated by them paravertebral injections of procaine alcohol are indicated

In three patients with a combined aortic insufficiency and stenosis who suffered from hypertensive crises and severe angina pectoris marked relief was obtained by the administration of thiouracil Four tablets of 0 1 Gm were given daily (Scherf and Terranova 1945) Within 4 to 7 days the patients claimed that they were able to sleep for the first time in weeks the symptoms recurred soon after the thiouracil was replaced by a placebo of the same size taste and appearance The patients felt better again when treatment with thiouracil was reinitiated

ANGINA PECTORIS IN OTHER CONDITIONS

SEVERE ANEMIA

Severe chronic anemias may be associated with serious changes in cardiac function and also with exertional angina pectoris (Herrick and Nuzum) The increased heart rate the greater output the acceleration of blood flow and better oxygen utilization compensate to a large extent for the lack of hemoglobin in advanced anemia This compensation is not ideal for sooner or later the heart suffers

The Heart in Chronic Anemia

Anatomically a fatty degeneration of the myocardium develops particularly in the area around the papillary muscles the area most sensitive to the lack of blood supply This combined with the increased activity of the heart is responsible for cardiac dilatation and hypertrophy Patients with marked dilatation of the heart secondary to anemia are rare nowadays but it still happens that patients with a severe chronic anemia are treated for a long time as cardiacs

Examination of these patients may yield a host of findings The peripheral arteries show a collapsible pulse Duroziez s murmur and a pistol shot sound a capillary pulse may be found Palpation of the precordium discloses cardiac hypermotility Percussion and x ray examination show enlargement of the right and left ventricles with mitralization the result of dilatation of the pulmonary artery and of the left atrium The enlargement does not parallel the degree of anemia and disappears after successful treatment It is absent despite a chronic advanced anemia in bedridden and cachectic patients (Zdansky) The pulsations of the heart are often found accentuated during fluoroscopic examination

A variety of abnormal findings are found on auscultation Tachycardia is usually present Splitting of the first heart sound imitating a presystolic murmur is followed by a loud first sound as in mitral stenosis This presystolic murmur is never drawn out it is very short and probably owes its appearance to the

activity of hyperactive atria It has been pointed out before that the atrial contraction causes a split sound to appear this may be confused with a pre systolic murmur Systolic murmurs over all orifices are the rule and occur mainly because of the increased speed of blood flow Over the apex there may be another loud systolic murmur when the left ventricle undergoes progressive dilatation and a relative mitral regurgitation appears An expansile liver pulse and a positive venous pulse in the neck indicate the presence of a relative tricuspid insufficiency In a few cases high pitched diastolic murmurs are heard at the base of the heart Sometimes they are due to a relative aortic insufficiency sometimes to the speed of blood flow in the veins In this instance the murmurs create a continuous hum with diastolic accentuation the latter is produced by the rapid flow of blood in the large veins close to the heart during diastole

Edema and hepatic enlargement appear in such patients and the mis interpretation of these cases as examples of rheumatic mitral or aortic lesions *formerly was a common occurrence*

Angina Pectoris in Chronic Anemia

Not rarely these patients complain of anginal pain on exertion However this distress is rarely of sufficient severity for the patient to mention it spon taneously Usually it is necessary to ask direct questions about it In one series of 1560 cases of pernicious anemia angina on effort was recorded in 2 7 per cent (Willius and Griffin) while in another series of 25 cases with a hemoglobin under 50 who were asked directly about angina pectoris on effort the symptom was present in eight (Pickering and Wayne)

In a large percentage of patients with anemia and angina on effort it is not the anemia alone but its combination with coronary sclerosis that causes the pain It is understandable that a coronary sclerosis insufficiently advanced by itself to provoke effort angina may do so when a severe anemia is superimposed Nevertheless instances are known in which an effort angina and severe anemia were associated although necropsy revealed normal coronary arteries

PAROXYSMAL TACHYCARDIA

It has been known for a long time that pain appears in the cardiac region or behind the sternum and radiates to the left arm in patients with paroxysmal tachycardia This pain is not always a minor symptom accompanying paroxysmal tachycardia or paroxysmal fibrillation with a high ventricular rate At times pain is so prominent that the false diagnosis of coronary thrombosis is made This mistake is understandable if the patient relates that he suffered from excruciating retrosternal pain lasting for several hours that radiated to the left shoulder and into the left arm The pain usually lasts as long as the tachycardia The relief afforded by nitroglycerin is temporary Since the increased heart rate is often not felt by the patient during the paroxysmal tachycardia pain alone is mentioned

If the paroxysmal tachycardia recurs pain reappears In one case of paroxysmal atrial fibrillation precipitated by reflexes whenever the patient took a deep breath (Burak and Scherf) pain developed for the duration of the fibrillation which was a few seconds or minutes this patient was treated as an effort angina until the nature of the pain was discovered Quinidine prevented the attacks of fibrillation and the anginal pain did not recur

The absence of the usual signs of a coronary occlusion and myocardial infarction following a prolonged attack of pain permits the differential diagnosis There will be no progressive fall of blood pressure and no increase of sedimentation rate It is necessary however to stress that a slight rise of temperature for a few hours hemoptysis and vomiting occur during some attacks of paroxysmal tachycardia

The great reduction of the minute volume during an attack of tachycardia and the decided fall of blood pressure coinciding with the remarkable increase of demand for blood by the heart explains the pain in patients with healthy hearts In patients who already have coronary sclerosis — that is in the majority of those beyond the age of 50 and in those who have a syphilitic stenosis of the coronary ostia — pain is more common during a paroxysmal tachycardia It may be agonizing In one case of syphilitic aortitis which came to necropsy shortly afterward there was narrowing of one and occlusion of the other coronary orifice This patient had to be given injections of morphine whenever a paroxysm of atrial fibrillation appeared with a ventricular rate of 190

Immediately after the onset of a paroxysmal tachycardia evidence of myocardial anoxia may be visible in the electrocardiogram for a short while after the tachycardia subsides abnormal T waves indicate the myocardial damage created by the increased rate (Burak and Scherf) This phenomenon has been named post tachycardia syndrome It was mentioned previously that mere acceleration of the cardiac rate by an injection of atropine in a patient with coronary stenosis may lead to marked alterations in the electrocardiogram

The differential diagnosis between paroxysmal tachycardia and coronary occlusion will be especially difficult if the patient is examined only after the tachycardia has disappeared At that time it may be impossible to ascertain the true cause of the pain Despite the negativity of all findings coronary occlusion with myocardial infarction cannot be completely ruled out

Obviously the prognosis and treatment of this type of angina pectoris is quite different from that of other forms The administration of sufficient doses of quinidine will effect a cure

HYPER AND HYPOTHYROIDISM

It is not unusual to encounter the typical pain of angina pectoris in hyperthyroidism Usually the pain occurs on exertion or excitement but it is reported to have occurred at rest and during the night The combination of anginal pain

cardiac disease and hyperthyroidism is uncommon before the age of fifty years (Lev and Hamburger) Presumably these patients have coronary sclerosis which alone would not cause angina pectoris When it is associated with the tachycardia and cardiac hypermotility dependent upon hyperthyroidism however the anginal pain appears on effort or excitement

Subtotal thyroidectomy or treatment with thiouracil or radioactive iodine usually affords excellent results

Coronary sclerosis is a common event in myxedema Many patients without previous symptoms develop anginal pain shortly after taking thyroid preparation Sometimes treatment with thyroid is impossible because pain recurs even when very small doses are used

PULMONARY EMBOLISM

Reference was made to the occurrence of angina pectoris in pulmonary embolism in previous sections

Pulmonary embolism may produce many of the symptoms and signs of coronary thrombosis Both may present pain lasting for hours fall of blood pressure and leukocytosis Fever increased sedimentation rate and alteration of the electrocardiogram follow so that the differential diagnosis between the two conditions is fraught with difficulty or may even be impossible Naturally pulmonary embolism rather than coronary thrombosis should receive primary consideration in a bedridden or postoperative patient unless cardiac symptoms suggestive of coronary disease have long been conspicuous To be sure both coronary thrombosis and pulmonary embolism may occur in seemingly healthy individuals without premonitory symptoms An earlier venous thrombosis may have entirely escaped recognition This situation prevails particularly when a traumatic thrombosis develops asymptomatically in a vein of the lower extremities some time after a slight and forgotten trauma

Attention has been previously directed to the fact that the pain associated with pulmonary embolism may last only for a few minutes and it may respond quickly to nitroglycerin The pain may recur repeatedly

CHEST PAINS IN CLIMACTERIC WOMEN

A precordial pain which occasionally radiates into the left arm is a common complaint in patients in the climacterium The symptom is described with great vivacity and is associated with considerable anxiety but it is not related to effort or other ascertainable extrinsic factors

Since objective findings such as hypertension tachycardia and electrocardiographic findings coexist confusion with the angina pectoris of coronary sclerosis occurs This subject will be discussed in a later chapter

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Chapter 17

Cardiac Changes due to Non-penetrating Trauma

THE DEVELOPMENT OF THE AUTOMOBILE increased expansion of industry and the simultaneous improvement of methods of clinical examination have contributed to the increasingly frequent occurrence and discovery of cardiac changes due to blunt trauma Abundant casuistic material that reaches back over a long period has been summarized by Warburg Experimental work on this subject was performed many years ago (Kulbs) but the important results were neglected until interest was revived by new contributions

One speaks of cardiac commotion when a patient dies after an accident involving a blow to the chest in the region of the heart and at necropsy not even a microscopic sign is found In contusion of the heart pathologic changes are visible

Etiology

The accidents responsible for cardiac changes are diverse Stumbling against a sharp object or a fall from a great height partial burial in sand during an excavation steering wheel accidents and chest injury caused by a blow from a rapidly moving object (baseball stone) exemplify some common occurrences It is important to note that cardiac trauma need not necessarily require a pre cordial injury (Bright and Beck) for the heart can rupture when the lower half of the body is exposed to severe pressure in a sandpit When the abdomen and lower extremities are compressed large quantities of blood may be pressed toward the heart and may overfill the chambers the right atrium is commonly ruptured although this may happen to any cardiac chamber Infarction of the posterior wall of the left ventricle has followed fracture of the sternum (contre coup force) Posterior wall lesions as a consequence of blows against the anterior chest wall are frequent in experiments If the elastic chest wall is pushed in by an accident the heart may be pressed between the anterior chest wall and the spinal column

Pathology

Pericardium All three layers of the heart may be injured The most common gross change is the presence of petechiae and hemorrhages in the epicardium Frequently the pericardium is ruptured even when the compressing force was

applied to the abdomen or lower extremities Traumatic pericarditis is not rare and in non penetrating myocardial injuries it appears as a consequence of sub epicardial myocardial damage with necrosis and reactive inflammation Thus it parallels the pericarditis observed after myocardial infarction Hemorrhagic pericardial effusion results from cardiac trauma Secondary calcification occurs

Myocardium The myocardial hemorrhages may extend over a large area Necrosis and softening may appear and perforation of the cardiac wall may follow immediately or after several days In experiments the conus area of the right ventricle is often involved (Scherf and Terranova)

The necrotic areas are often multiple and may be found in all parts of both ventricles A rupture caused by necrosis of the right atrium is most common but any chamber or the interventricular septum may be involved In the injured area edema and disorganization of the muscle bundles with migration of polymorphonuclear leukocytes can be observed within twenty four hours (Moritz and Atkins)

It is important however to emphasize that in a large percentage of acute experiments with a fatal outcome no changes were found at post mortem In experiments on 25 cats anatomic changes were missed in 15 animals despite a fatal ending and the presence of marked electrocardiographic changes Ventricular fibrillation did not occur (Scherf and Terranova) In the hospital wards the same observation may be made A 26 year old man died immediately following a blow over the cardiac area during boxing no abnormality was found at post mortem (Deutsch)

Endocardium Subendocardial petechiae are often seen Rupture of the valves due to direct or indirect trauma has been described frequently the aortic valve is affected more often than the mitral Valvular rupture following slight trauma is prone to occur when the valve is already diseased This is illustrated by the rupture of an aortic cusp and traumatic aortic regurgitation in syphilitic aortitis an accident that is not particularly rare following unusual strain The diastolic murmur appearing in these traumatic aortic insufficiencies is usually musical

Symptoms and Signs

Sudden death may follow blunt trauma of the heart immediately or several weeks after the accident Often patients faint or have severe pain or palpitation extreme weakness may be present Pain may not appear for several hours or even days after the accident however and when late it is often due to the appearance of pericarditis The frequent statement that symptoms must appear instantly or very soon after the accident in order to connect the cardiac damage to the trauma is certainly true in a majority of cases but it is not invariably applicable

In clinical cases and in experiments a marked drop in blood pressure acute dilatation of the heart gallop rhythm and embryocardia (tic tac rhythm) may follow an accident

Since large areas of the heart muscle may become necrotic symptoms and signs may closely resemble those of coronary thrombosis with myocardial infarction Fever fall of blood pressure leukocytosis and an increased sedimentation rate are present There is collapse shock pallor sweating The heart sounds may be faint Mural thrombi and emboli may develop In other cases few symptoms are present In many instances particularly with rest complete recovery takes place Perforation of the septum has been reported Sudden death may occur several weeks after the accident

The myocardial necrosis following blunt trauma may lead to chronic heart disease in the same way that myocardial infarction following coronary occlusion

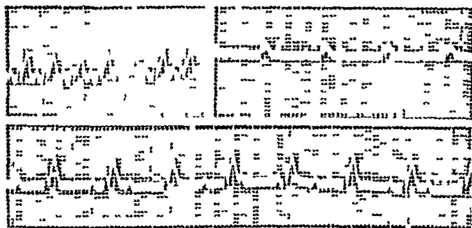


FIG 84 An experiment on a cat A heavy blow was struck on the anterior chest wall Immediately the normal electrocardiogram changes to one with complete A V block and monophasic QRS complexes (high take off) Four minutes later the lowermost tracing was obtained the monophasic electrocardiogram has given place to normal QRS complexes but the heart block persists The first upper (normal) tracing is lead II the other two are lead III (Scherf and Terranova)

lead to chronic heart disease Chronic ventricular aneurysm may appear An existing heart disease may be aggravated

It is important to re emphasize that serious damage and even rupture of the heart sometimes follows blunt trauma in the absence of a visible external injury (Hamilton Kellert)

Arrhythmias Variform arrhythmias are very common They are often observed clinically and experimentally The simplest and most common type consists of extrasystoles which may arise in any part of the heart Sinoatrial block and atrioventricular rhythm also occur Atrial and ventricular fibrillation paroxysmal atrial and ventricular tachycardia and any type of partial as well as complete heart block have been observed (figure 84) These changes stem partly from hemorrhages and necrosis but temporary mechanical irritation of the muscle fibers also plays a great part

Electrocardiogram Electrocardiographic changes are very common an electrocardiogram should be taken in every accident in which cardiac involvement might be present

In addition to arrhythmias the electrocardiogram may show changes due to pericardial and to myocardial damage The alterations of the QRS complex and T waves resemble those of other myocardial lesions Even a high take off similar to the one of coronary thrombosis has been observed This was ascribed to coronary spasm induced by the mechanical irritation of the coronary arteries (Schlomka) but the high and low take off appears with the first beat after the trauma much too soon to be explained by coronary artery spasm Such changes are better explained by a direct mechanical derangement (depolarization) of the superficial muscle layers resulting from the blunt trauma (Scherf and Terranova) Similar transient changes are encountered after mechanical irritation of the exposed heart They disappear within minutes (Boyd and Scherf) Since mechanical irritation of the coronary vessels as in the case of other arteries may be followed by local vasoconstriction (Drury and Smith) a local coronary spasm is not impossible in some cases This can only cause secondary changes appearing 40 to 60 seconds following the trauma

The physician should always think of the possibility of a laceration of the heart particularly of the right atrium in direct compression of the abdomen Lives are saved by the correct diagnosis and successful suture of the atrium (Desforges et al)

CORONARY THROMBOSIS AND TRAUMA

A question of great interest and importance is the possible appearance of coronary thrombosis following non penetrating trauma Clinical cases in which coronary thrombosis developed after an accident have been reported in increasing numbers in recent years Possibly such accidents result from rupture of a giant capillary in a sclerotic coronary artery or a rupture of an atheromatous abscess Exact data to prove this occurrence do not exist Usually a relation is assumed if the symptoms and signs of a coronary occlusion appear immediately after or shortly after a trauma but as mentioned earlier symptoms and signs may not develop for hours Since trauma causes myocardial necrosis at times over a large area without involvement of the coronary arteries it is difficult to differentiate between myocardial infarction due to coronary occlusion and myocardial necrosis resulting from contusion of the heart As pointed out before most of the signs may be identical in both instances

The history has paramount importance in establishing the connection between an accident and the cardiac involvement While the appearance of a coronary occlusion following precordial trauma and compression of the chest wall in the antero posterior direction in cases with coronary sclerosis is very probable although not established beyond all doubt the occurrence of a coronary occlusion from abdominal trauma or after lifting heavy objects is dubious although not impossible

On the other hand a case has been observed in which a helper on a truck suffering an attack signalled the driver to stop and then collapsed on the floor of the truck The driver swung out of traffic but in so doing dislodged part of the load which fell upon the already stricken helper

X RAY THERAPY ELECTRICAL ACCIDENTS

Very serious myocardial damage is frequently observed following deep x ray therapy (or radium implantation) in the cardiac area We saw repeated evidence of cardiac failure with tachycardia gallop rhythm and pulmonary congestion develop following deep x ray therapy for Hodgkin s disease or mediastinal malignancy

Pericardial irritation due to x ray irradiation has been mentioned

A voluminous literature exists on experimental and clinical observations of atrial and ventricular fibrillation in connection with electrical accidents

Therapy

Treatment consists of bed rest symptomatic measures and in the case of cardiac rupture surgery Since many cases of serious myocardial lesions are reported to follow comparatively minor trauma and since persistent searching more and more frequently turns up evidence of traumatic cardiac lesions it seems advisable to examine electrocardiographically and by x ray every patient involved in such an accident Bed rest should be continued until cardiac involvement can be definitely eliminated Early signs of cardiac tamponade should be looked for

While recoveries were rare in cases reported by the original investigators their number increases with careful observation Originally only very serious cases with cardiac rupture traumatic aneurysm and the like were reported but at present milder injury is often described Chronic heart disease with long invalidism does occur

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Chapter 18

The Heart in Endocrine Disorders

Hyperthyroidism

Hyperthyroidism can disturb cardiac action very profoundly but the alterations are not invariable nor when present do they always develop with the same speed and to the same degree Sometimes patients manifest all features of hyperthyroidism but display no evidence of cardiac involvement save for an insignificant tachycardia Even this may be absent On the other hand patients with an apparently mild hyperthyroidism may develop cardiac dilatation and evidence of congestive heart failure within a short time

Incidence

The affection is more common in women than in men Its incidence varies considerably in different localities being most frequent in the Great Lakes basin of the United States and in the Alpine regions of Europe It occurs at all ages we have encountered it in children of five years and in people beyond seventy

Pathology Pathophysiology

At necropsy about 50 per cent of patients dying from hyperthyroidism show cardiac hypertrophy and dilatation These changes may be absent even in very toxic cases and they are uncommon in elderly cachectic patients who have lost much weight There is no parallelism between cardiac size and degree of hyperthyroidism

The mechanism of cardiac enlargement is obscure In some cases it may be explained by the presence of a coronary atherosclerosis a complicating hyper tension or atrial fibrillation that was untreated or that failed to respond to treatment It occurs however without these complications

The increased rate hardly contributes to the changes but the increased motility which seems to result from a direct action of thyroxin on the myocardial fibers and the increased load on the heart may tire the muscle and lead to dilatation Histologic examination fails to reveal characteristic or consistent lesions physico chemical changes that are not revealed by histologic examination may be responsible Contrary to the frequently expressed opinion it is note worthy that cardiac enlargement and failure may be found in young people or even adolescents with pure hyperthyroidism without other demonstrable compli

cations Naturally a patient with a slight rheumatic lesion coronary sclerosis or syphilitic heart disease tends to develop decompensation earlier if hyper thyroidism coexists In 176 fatal cases congestive heart failure existed 27 times in a majority of these complications such as coronary sclerosis rheumatic heart disease and syphilis were found (Kepler and Barnes)

Symptoms

The symptoms of thyroid hyperfunction will not be discussed here The dyspnea is partly due to increased metabolism and rarely to pulmonary congestion Sighing respiration is often responsible Palpitation is a very common complaint and is evoked by the marked cardiac hypermotility or paroxysmal fibrillation Attacks of paroxysmal atrial fibrillation are often observed Angina pectoris occurs as was mentioned before, it is found only in elderly patients who in addition to hyperthyroidism also suffer from coronary disease

Signs

The description of the signs will be limited to those of the cardiovascular system

Palpation Extremely powerful quick pulsations over the precordium may shake the whole thorax and suggest a much larger heart than actually exists These pulsations are most easily palpable near the conus of the right ventricle

While an increased pulse rate is usually present it is not rare for a normal sinus rate or even bradycardia to occur Often the pulse has all the characteristics of a water hammer pulse as in aortic insufficiency

Blood Pressure The pulse pressure occasionally shows a marked increase since the systolic pressure may rise to 180 mm Hg or more and the diastolic pressure often drops to below 50 mm Hg This thyrotoxic systolic hypertension is caused by the hypermotility of the heart

Percussion and X ray Examination Percussion reveals a normal or a mitralized heart dilated to the right and left The incidence of dilatation is higher in patients with old and advanced hyperthyroidism and with other complications Therefore the figures vary with the clinical material It is least common in areas where the diagnosis is made early and therapy is employed quickly

Fluoroscopy reveals marked hypermotility of the heart and pulsus celer of the aorta The pulmonary artery is dilated in one third of the patients This is probably not due to constitutional factors as has been stated nor to persistence of juvenile conditions but rather to a dynamic dilatation caused by the hyper motility of the right ventricle The aorta may also show dynamic dilatation In hyperthyroidism with heart failure the lung fields are clear as the right ventricle dilates and fails from the start

Auscultation Often the heart sounds are abnormally loud A short pre systolic click caused by the contraction of the hyperactive atrium may cause

confusion with mitral stenosis Systolic murmurs are very common over the pulmonary artery and aorta and are due to the increased speed of blood flow Extracardiac venous murmurs like those present in anemia are frequently heard If they appear in diastole and the peripheral pulse is of the Corrigan type the erroneous diagnosis of aortic insufficiency may be made In a patient with hyperthyroidism seen by one of us a large adenomatous nodule that compressed the left subclavian artery produced a double Duroziez murmur at the left sternal border imitating an aortic insufficiency The increased speed of the circulation causes a diastolic venous hum over the large veins A pericardial friction rub is not rare over the prominent conus of the pulmonary artery It results from the friction between normal epicardium and normal pericardium and should not be mistaken for a real pericarditis Relative aortic insufficiency has been described but it is possible that a diastolic murmur in these cases was evoked by one of the mechanisms just mentioned

Electrocardiogram The electrocardiogram does not help in the diagnosis It is normal or shows only sinus tachycardia Abnormalities of the T waves are rare Depression of the RS T segments is noted occasionally

Laboratory Tests The serum protein bound iodine permits an estimation of the level of the circulating thyroid hormone Also useful is the determination of the level of radioactive iodine uptake with tracer doses of I^{131}

Complications

Hepatic enlargement and edema appear late Atrial fibrillation is a common complication but its appearance in hyperthyroidism has not as yet been fully explained It often occurs in short paroxysmal attacks but soon becomes constant unless abolished by successful treatment of the hyperthyroidism Due to the high sympathetic tonus the ventricular rate is rapid and characteristically the rate does not slow quickly under treatment with digitalis Extrasystoles are not very common an astonishing fact in view of the great frequency of fibrillation

Differential Diagnosis

The diagnosis is very easy in typical cases but may be difficult in others In mild cases the presence of low fever cardiac symptoms and signs may lead to the diagnosis of rheumatic heart disease or subacute bacterial endocarditis In very advanced cases the cardiac enlargement and right ventricular failure suggest the diagnosis of a decompensated mitral lesion In the latter condition the left atrium usually is markedly dilated whereas it is normal or only slightly enlarged in hyperthyroidism the differentiation is sometimes difficult The situation is rendered more confusing since in cardiac lesions an increased basal metabolic rate of 50 per cent or more is not rare and other signs of hyperthyroidism such as wasting excitability and tremor may also appear Finally it may be difficult to distinguish between mild hyperthyroidism and cardiac neurosis

Physicians must always be on the alert not to overlook masked hyper thyroidism appearing as atrial fibrillation of the chronic or paroxysmal type heart failure and the like

In many cases the evidence of cardiac involvement is so much in the foreground that the attending physician overlooks the hyperthyroidism which is the etiologic factor and treats the patient symptomatically only for his cardiac complaints With more careful examination and with consideration of the hyperactivity of the patient his nervousness his inclination to perspire easily and so forth the correct diagnosis will be made

Treatment

As soon as hyperthyroidism is recognized specific therapy should be started This may be accomplished with the methods of bloodless surgery that became available in recent years Propylthiouracil is given daily (400 mg) in 100 mg doses with continuous supervision of the white blood cell count As soon as improvement is noted the dose is reduced to 50—100 mg daily Tapazole (mercapto imidazole) may be given initially in doses of 40 mg daily and later 5—20 mg daily Skin irritation and fall of the leukocyte count occasionally preclude continuation of the treatment

Within three months after the discontinuance of this therapy a relapse may be expected in 23 per cent of the patients In another 20 per cent relapses occur later A lasting effect is accomplished in only about 50 per cent of the cases with one series of treatments

Therapy with radioiodine has a much larger percentage of permanent success It is the method of choice in the elderly patient

Surgery is indicated for hyperthyroidism alone if for certain reasons the patient cannot undergo medical therapy

Signs of hyperthyroidism are not rare in the climacterium and they complicate the picture (see below)

HYPOTHYROIDISM

Just as the cardiac alterations may be surprisingly slight despite marked hyperfunction of the thyroid there are instances of marked hypothyroidism with a basal metabolism more than 30 per cent below normal with normal circulatory findings It is unknown why cardiac abnormalities appear early in one case and are absent in another The infrequency of cardiac abnormalities in a fair percentage of cases was the chief reason the existence of a myxedema heart was often denied in the past

Symptoms

In an uncomplicated case of myxedema with marked cardiac involvement there are no typical cardiac complaints The lassitude and general weakness are not characteristic and it is uncommon for the patient to seek advice for dyspnea

or edema However a complicating angina pectoris due to coronary sclerosis often causes the patient to ask for medical assistance

Signs

The heart may be enlarged to the right and left Marked flatness is often percussed over the precordium On fluoroscopy the pulsations of the cardiac borders are sluggish and in some patients the borders scarcely move The heart sounds are muffled and distant Rough systolic murmurs over the aortic or mitral valve when present are due to atherosclerotic changes The blood pressure is normal or moderately elevated Bilateral or right sided hydrothorax is common

In a typical uncomplicated case the electrocardiogram shows low voltage of all waves in each lead the P and T waves may disappear completely and the QRS complexes are often only a few millimeters in height

Differential Diagnosis

Few diseases are so often overlooked as myxedema Errors occur even in fully developed forms with typical alterations in the skin puffiness of the face the deep harsh voice sensitivity to cold slow motor and psychic reactions in which the diagnosis should be apparent at a mere glance Most often some intrinsic cardiac disease is diagnosed because of the finding of cardiac enlargement edema hepatic enlargement and electrocardiographic abnormalities Very often these patients have been subjected to long courses of digitalis which afforded no relief The albuminuria and facial edema may lead to a diagnosis of nephritis The accompanying anemia leads to liver and iron therapy and often the headache and constipation are treated symptomatically without the basic malady being recognized

Pathology

Formerly the cardiac alterations were ascribed to myxedematous swelling of the myocardial fibers Histologic examination often shows fibrosis or degeneration of these fibers but in many cases this is due to the coexisting coronary sclerosis in any event these changes are not pathognomonic In recent years an increasing number of observations indicate that a pericardial effusion is present in a large percentage of cases Pericardial effusions are observed after thyroidectomy in sheep goats and rabbits The diagnosis of a pericardial effusion was confirmed by paracentesis in eleven patients seen by us in recent years The flatness over the precordium the sluggish contractions of the heart on fluoroscopy and the low voltage in the electrocardiogram are easily explained by a pericardial effusion To be sure sluggish contractions also occur in myocardial lesions but rarely to an equal degree unless the heart muscle has suffered unusually severe damage Moreover a pericardial effusion more readily explains the rapid restoration of normal cardiac diameters following the administration

of thyroid substance In a myocardial disease it is rare for one to observe a markedly enlarged heart return to normal size with equal speed and to a similar extent

Pericardial effusions with a very high content of cholesterol in the pericardial fluid occur in the absence of myxedema and with a normal blood cholesterol level their origin is still unexplained

To what extent the cardiac enlargement must be attributed to a pericardial effusion in a given case of myxedema is often difficult to ascertain

Complications

The most common and most important complication of myxedema is coronary sclerosis This is a regular event in chronic cases and is presumably connected with the hypercholesterolemia Some electrocardiographic findings in myxedema such as abnormal T waves and a prolonged P P interval as well as the cardiac enlargement and fibrosis on histologic examination are due to coronary sclerosis and not to myxedema Owing to this complication patients with myxedema often develop angina pectoris Coma as well as maniacal excitement occur (Summers)

Treatment

Great care is necessary in therapy with thyroid substance or thyroxin Often the doses used are excessive and much harm can be done One tablet of 0 01 Gm thyroid given daily often suffices sometimes smaller doses must be given *The patient should be watched continuously since the cardiac situation* may become worse as the metabolism reverses to normal although the myxedema is improved the increased heart rate and increased oxygen consumption of the heart may be injurious in the presence of coronary sclerosis Frequently it will be found more advantageous to allow the patient to retain a low metabolic rate than to treat the myxedema and initiate severe attacks of angina pectoris Occasionally we have seen angina pectoris on effort disappear following the administration of thyroid extract

Like hyperthyroidism myxedema may develop during the endocrine imbalance of the climacterium

OVARIAN HYPOFUNCTION AND THE FEMALE CLIMACTERIUM

Incidence

Few women are entirely free from complaints during the climacterium An inquiry among 1000 women of all ages revealed that only 15 8 per cent went through the critical age without annoying symptoms (Council) In another series of 1000 cases symptoms were found in 85 per cent (Hawkinson) Many suffer from a host of disturbances and not a few are even incapacitated (10 3 per cent)

Among the diversified symptoms cardiovascular complaints are very common In 1000 women tachycardia palpitation and dyspnea occurred in 70 per cent (Hawkinson) Another observer found the same symptoms in 68 8 per cent of his patients (Werner) About 22 per cent of all women coming to a cardiologist for advice have complaints referable to disturbances of the activity of the ovaries Substitution therapy affords complete relief

Symptoms

General Emotional instability irritability and exhaustion are the chief symptoms in many cases and mental disturbances similar to those of involutional melancholia may occur In other patients gastrointestinal or cardiac complaints are in the foreground Still others have rheumatic pains complaints due to osteoporosis sleeplessness and dizziness

Hot Flushes The outstanding complaint in about 60—85 per cent of the patients is the flush Sometimes after a slight aura consisting of nausea the patient feels a wave of heat ascend to the face and arms immediately followed by a chill and cold sweat The developmental mechanism of this complaint which is not found in any other condition is not as yet fully explained

Dyspnea Many women suffer from the three classical complaints of cardiac patients dyspnea palpitation and cardiac pain The dyspnea may be very pronounced Detailed questioning soon reveals that it consists of a peculiar inability to get the breath through the sighing respiration discussed in the first chapter Only after obtaining information from the doctor does the patient recognize the sighing respiration as the reason for her breathlessness A few explanatory words will go very far to relieve the patient from the extreme apprehension connected with this sensation

Palpitation The palpitation of these patients is independent of exertion and excitement and lacks the characteristic features of the palpitation of a paroxysmal tachycardia that is of sudden onset and ending Often it occurs together with the hot flushes the association is particularly common at night

Pain Pain in the cardiac area is the third important symptom to make the patient heart conscious and apprehensive The pain appears over the precordium (not behind the sternum) and sometimes spreads to the left shoulder and left arm It is not provoked by exertion or excitement and it may last for hours In a majority of these patients examination reveals an area of exquisite tenderness at the fourth (more rarely fifth) rib to the left of the sternum at the costochondral junction (Scherf and Klotz) Rarely the tenderness is found at the fourth and fifth rib of the same patient Infiltration of this small spot with procain affords immediate relief It is possible that local arthritic (osteochondritic) or arthralgic changes account for this complaint as is the case in other menopausal arthralgias According to Staehelin inflammatory processes of the cartilages of the ribs are not rare The connection with ovarian dysfunction is proved by the disappearance of the pain in a few weeks following the administra

tion of sufficient doses of estrogen These complaints are easily separated from those in Tietze's syndrome with marked swellings of the cartilages

Other Symptoms In addition patients often complain about paraesthesias such as numbness and tingling in the fingers and toes as well as headaches Vertigo is common Insomnia abnormal worrying weeping edema of the face foot and calf are not rare

Signs

Sometimes examination reveals nothing abnormal save the sighing respiration and the circumscribed tenderness over the fourth rib In other patients however objective findings are present

The heart may show a marked hypermotility even when there is no evidence of hyperthyroidism A sinus tachycardia up to 120 may be present There may be a moderate hypertension and the electrocardiogram occasionally shows changes of the RS T segments and abnormal T waves (Scherf) Estrogens disappear from the urine and the amount of gonadotropic hormone increases

Hypertension The question of a climacteric hypertension has vexed workers and the subject is controversial Some authorities find the blood pressure elevated in as many as 50 per cent of the cases while others regard any increases of the blood pressure during the climacterium only as a coincidental and unrelated finding (Pal) Since most of the women concerned are at an age in which the blood pressure is often elevated a decision is difficult On the other hand patients with the syndrome described and hypertension so often have the blood pressure fall to normal levels during treatment with estrogen that a relation cannot be denied Such patients are seen more often in private practice than in the hospital In many cases hypertension disappears within a few weeks following the administration of estrogens while in others prolonged treatment is necessary Marked fluctuation of the blood pressure is common In this and other types of hypertension if the blood pressure stays at a high level for some time it becomes fixed and estrogen treatment will not lower it but will only alleviate some symptoms

Taylor et al examined 179 castrated women and 21 with a natural menopause and found that within a three year period hypertension occurred in the same incidence as in the general population This merely emphasizes a fact known for a long time namely that the lack of the estrogenic hormone per se does not cause hypertension The imbalance of the endocrine glands (hypophysis adrenals) may cause hypertension years afterward This occurs sometimes more than three years after panhysterectomy

Women in whom panhysterectomy was done 5—10 years previously occasionally suffer from fixed hypertension Due to the absence of symptoms these patients reach the physician too late In our opinion the blood pressure of women after panhysterectomy should be checked at regular short interval for at least 10 years after the operation and estrogenic treatment should be administered as soon as it is indicated Borgstroem reports excellent results of treatment with estrogenic and androgenic hormones in essential hypertension

Electrocardiogram The electrocardiographic changes do not depend upon the presence of a hypertension and are independent from an existing hyperthyroidism They disappear promptly after the administration of estrogens in sufficient doses

Figure 85a shows the electrocardiogram of a 54 year old woman who developed flushes paraesthesias palpitation and precordial pain The heart showed a marked hypermotility and the blood pressure was 160/90 mm Hg The electro

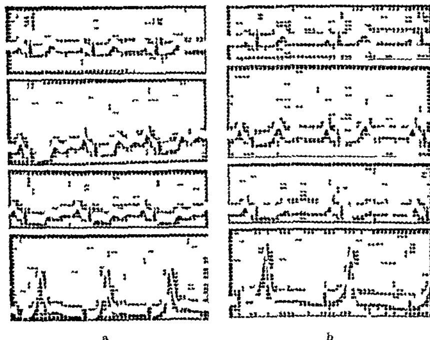


FIG 85 A 54 year old woman presenting the climacteric syndrome before (a) and after (b) treatment

cardiogram shows a depression of the PS T segments in each standard lead and in CR4 The heart rate is 94 beats per minute

Following the daily administration of 0 5 mg of diethylstilbestrol for four weeks the electrocardiogram of figure 85b was obtained It shows a heart rate of 70 and normal RS T segments The symptoms disappeared and the blood pressure was 138/85

Atherosclerosis The more common occurrence of atherosclerosis in man as compared to woman has been known for many years Lately clinical and experimental observations speak for a protective action of the estrogenic hormone Women following natural or artificial menopause show atherosclerosis more frequently than women who are normally menstruating Experimental results were mentioned in a previous chapter Oliver and Boyd found that small doses of ethinyl estradiol depressed plasma ester cholesterol in men This compound has an antiatherogenic action

Pathogenesis

Vascular Effect It is still impossible to explain how these changes originate Since female sex hormones seem to be vasodilators since paraesthesias and acrocyanosis appear in these patients and since vasodilators help the changes may rest on a vascular basis

Electrolytes It is also known that sex hormones like other steroids have a great influence on the electrolyte metabolism particularly on sodium and calcium metabolism It is thus possible that the electrocardiographic alterations can be explained by tissue changes induced by an abnormal electrolyte balance The arthralgias as well as other manifestations of the climacterium may also be caused by one or both of these mechanisms

Hormonal It seems generally agreed that diminution or cessation of normal ovarian function leads to overactivity of the anterior hypophysis the dissenting opinions are in the minority The response of the pituitary leads to oversecretion of the thyrotropic and adrenotropic hormone and results in abnormal function of these glands The resulting clinical pattern as well as the complaints of the patient depend upon the balance of the endocrine system and the status of the patient s autonomic nervous system There is suggestive evidence of a hyper sensitivity of the sympathetic nervous system in the menopause

Estrogen deficiency alone is not responsible Panhysterectomy in young women is often unassociated with symptoms Sometimes manifestations occur years later Flushes and other symptoms may be present despite remarkably high amounts of estrogens in the urine Estrogens may be found in women of 70 and more On the other hand flushes and other complaints may appear while menstruation is normal Probably the imbalance of the endocrine system causes the syndrome in a way which is still obscure

Diagnosis

Naturally in women with complaints referable to the heart with edema hypertension and electrocardiographic changes organic heart disease is often diagnosed We have observed such women put to bed for several weeks with a diagnosis of coronary occlusion or myocarditis sometimes digitalis is used because it is thought the patient is decompensated

It is necessary to emphasize that the climacterium and the menopause are not synonymous The characteristic flushes as well as other symptoms and signs mentioned previously may appear years before or after the cessation of menses They are not very unusual in girls 16 to 18 years of age if they have hypo ovarianism and they may be noted for the first time in women at the age of 70

If the physician attributes the complaints to a change of life the young patient may indignantly explain that she is still menstruating normally while the elderly one may find the diagnosis ridiculous because she has not menstruated for years

Organic Heart Disease and the Climacterium

It has long been the experience of clinicians that patients with an old fully compensated rheumatic valvular lesion or hypertension may develop decompensation during the climacterium In view of the alteration found in women with healthy hearts during the climacterium the increase of blood pressure and the tachycardia these events are understandable All these patients deserve careful supervision during this period and estrogens should be administered in sufficient dosage If this is done full compensation may be preserved for many years without other measures

Myoma (Fibroid) Heart

For many years the status of the heart in patients with uterine fibroids so called myoma heart was widely discussed in medical circles Time and time again changes were described and then challenged Some attributed the changes to the anemia to toxic or mechanical factors acting on the circulation while others found evidence of cardiac damage in the absence of these complications The diagnosis of myoma heart as a clinical entity was rightly abandoned In all probability most of the changes found in these patients are due to the mechanisms mentioned above since such tumors often develop or produce symptoms at the menopause or later

Treatment

The administration of estrogens usually affords striking improvement of the cardiac symptoms in a short time and causes the irritability of the patient to disappear The effect on the tachycardia hypermotility as well as on the hyperthyroidism and hypertension of these patients is equally satisfactory The help given to this group of patients is great

Oral medication usually will suffice Treatment must be persistent often for months occasionally for years In some patients a full therapeutic effect is attained with small amounts orally administered in others particularly those with marked hypertension parenteral therapy with large doses is necessary Inadequate dosage is a very common cause for therapeutic failures If treatment with estrogens becomes necessary in women who are still menstruating the preparations are best given for the first two weeks after the menstrual flow At a later period in the menstrual cycle estrogens may delay the onset of menstruation overdosage may prevent its appearance Often estrogen plus androgen mixtures are useful

The beneficial effect of estrogenic therapy has done a great deal to cause abandonment of the conception of a climacteric neurosis as the cause of complaints

The administration of nonhormonal estrogenic substances such as diethyl stilbestrol has the advantage of inexpensiveness While the action is satisfactory toxic effects occur

Before estrogens were available in large effective doses x ray radiation of the hypophysis was recommended in these patients this method has value in selected cases Sedatives like phenobarbital and chloral hydrate support estrogenic therapy in the early stages

Peripheral vasodilation has been reported following the administration of estrogenic substances and this led to their use in peripheral vascular diseases and angina pectoris Available evidence is still insufficient to establish their value in these patients However the effect of estrogens on the development of atherosclerosis is apparently established

Male Climacterium

In males cessation of gonadal function does not occur as suddenly as in females therefore the endocrine and autonomic nervous system have more time for adaptation to the new situation Many authorities deny the existence of climacteric symptoms in men We are convinced they do occur even to the extent of typical flushes with chills and sweating They are however rare Paraesthesias irritability sleeplessness and chest pain of the anginal type are observed The 17 ketosteroids in the urine tend to be low In these patients improvement has been observed after the administration of androgens (McGavack) Usually 25 mg per intramuscular injection twice weekly and a total of 10 or 12 injections are advised Normalization of the electrocardiogram of such patients follows The altered electrocardiogram of female patients with the syndrome discussed above may revert to normal also when male hormones or desoxycorticosterone is given (Scherf and McGavack) For the differentiation from neuroses Heller recommends a therapeutic test with androgens These bring about a rapid improvement in patients with the male climacterium

OTHER ENDOCRINE DISEASES

In this section brief reference will be made to cardiac and circulatory disorders in other endocrine disturbances Some of these changes have great theoretical interest but they are of minor clinical importance because other *manifestations* of the endocrine disorder are *in the foreground* Some of the lesions were or will be discussed in other chapters

In patients with an eosinophilic adenoma of the pituitary and acromegaly enlargement of the heart and cardiac failure is reported

In patients with basophilic adenoma of the pituitary and adrenal cortical tumor (Cushing s syndrome) hypertension and atherosclerosis are common

Diseases of the hypophysis or hypothalamus occasionally cause orthostatic hypotension

The syndrome caused by benign pheochromocytoma of the adrenals is discussed in the section on hypertension In Addison s disease an astonishing reduction of cardiac size is observed during the crisis due to a diminished quantity

of circulating blood (McGavack) Marked changes are found in the electro cardiogram as a consequence of the disturbances of electrolyte metabolism In hyperaldosteronism hypertension is the rule

Administration of excessive amounts of desoxycorticosterone may lead to cardiac enlargement and to evidence of pulmonary congestion (Paab)

In hyper and hypoparathyroidism alterations of a characteristic nature appear in the electrocardiogram and concern the length of the RS T segments caused by the altered calcium metabolism

Hyperfunction of the Langerhans islands due to adenoma or malignant tumor may lead to attacks of hypoglycemia which closely imitate attacks of coronary occlusion with anginal pain (Ernstene and Altschule) It has been pointed out that hyperadrenalemia as the consequence of hyperinsulinism may be responsible for this Hypofunction of the islands of Langerhans with hyper glycemia does not cause cardiac changes

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Chapter 19

Cor Pulmonale

COR PULMONALE IS NOT A DISEASE SUI GENERIS but a symptom complex always encountered when the right ventricle is subjected to increased demands because of hypertension in the lesser circuit The latter is caused by pulmonary vascular disease or deformities of the chest Increased pressure due to mitral valvular lesions or left ventricular failure is not included in this chapter Chronic emphysema with chronic bronchitis is the most common cause

A distinction is made between acute subacute and chronic cor pulmonale The acute form has been discussed with the syndrome of pulmonary embolism The subacute form is seen in status asthmaticus in chronic pulmonary embolization and in pulmonary carcinomatosis (lymphogenous or hematogenous spread) The chronic form is seen in a variety of lung diseases and abnormalities of the thoracic cage

Cor pulmonale is found to be a common condition if a careful search is made for it Clinical statistics showing its incidence are unreliable because the diagnosis is difficult The pulmonary disease is often overlooked and the patient is treated as a primary cardiac

Incidence and Pathology

Cor pulmonale occurs in conjunction with three groups of pathologic conditions

(1) Cor pulmonale may be present in subacute or chronic diseases of the pulmonary parenchyma Chronic bronchial asthma or chronic bronchitis emphysema and pulmonary fibrosis due to pulmonary tuberculosis pneumoconiosis and even bronchiectasis with recurrent pneumonias and infection often present the picture of cor pulmonale It may be seen in Boeck s sarcoid in sickling disease and in schistosomiasis Arvidson et al described four patients with pulmonary hypertension caused by malformation and stenosis of the branches of the pulmonary arteries

In addition to the well known forms of pulmonary fibrosis and pneumoconiosis the idiopathic interstitial acute diffuse fibrosis (Hamman Rich disease) should be mentioned Here extreme dyspnea and cyanosis with marked hyper

trophy of the right ventricle develop quickly within a few weeks There is slight fever and a moderate leukocytosis Hemoptysis and cough appear Postmortem examination reveals an inflammatory nonspecific process of unknown origin There is necrosis of alveolar epithelium with fibrin in the alveolar wall A virus infection has been suspected as an etiologic factor

(2) The picture of cor pulmonale develops in the rare type of essential (idiopathic primary) pulmonary hypertension Syncope occurs and sudden death is common Essential pulmonary hypertension for the most part is a syndrome encountered in women between the age of 20 and 30 years They complain of dyspnea pain on exertion palpitation fainting on effort and cyanosis There is evidence of marked right ventricular hypertrophy and dilatation the second pulmonic sound is very loud and there is no intrinsic pulmonary disease It is possible that in some of these patients minute pulmonary emboli that go unrecognized over years are responsible (Owen et al Barnard) Patients with essential pulmonary hypertension often die suddenly

(3) The same syndrome develops when respiration is disturbed by chest deformities Kyphosis does not lead to cor pulmonale On the other hand scoliosis does because of the emphysema and local infections leading to hypoxia In patients with a funnel chest the heart usually escapes compression by shifting to the left half of the chest and surgical intervention is rarely needed Right bundle branch block not rarely appears in the electrocardiogram Chronic bronchial or tracheal stenosis — the latter for example resulting from a nodular goiter — may also cause right ventricular hypertrophy the mechanical goiter heart In these patients the abnormal respiration alters the negative pressure within the chest and thus disturbs the chief factor aiding the return of blood to the heart Atelectasis and collateral emphysema appear and increase the pressure in the lesser circuit Disturbances of respiration also lead to an abnormal blood flow within the lung from the right ventricle to the left atrium

In emphysema it is not the loss of elasticity of the tissue and the closure of capillaries that leads to hypertension in the lesser circuit and to cor pulmonale Rather in all probability it is the narrowing of the vessels due to local foci of anoxia (as pointed out below) this explains why in many patients with emphysema the pulmonary pressure was found with catheterization to be normal Therefore all infections which lead to the secretion of mucus and occlude small air passages must be treated early with antibiotics Such infections need not cause fever (Flint) The precipitating cause of heart failure was an acute respiratory infection in 74 out of 76 patients with cor pulmonale Penicillin is given by injection and by aerosols in addition terpin hydrate aminophyllin potassium Vaponephrine (5–8 drops three times a day) and Isuprel (1 200 aerosol inhalation) are used The great fatigue is often caused by a relatively too small cardiac output A supporting lower abdominal belt is used and better movement of the diaphragm is accomplished by pneumoperitoneum In those patients who develop polycythemia phlebotomy is performed

Physiology

Normal pulmonary arterial systolic blood pressure varies between 15 and 25 mm Hg and the diastolic pressure is between 6 and 10 mm Hg The blood pressure in the lesser circuit does not rise even when more than 50 per cent of the pulmonary arteries are ligated

Anoxia causes an increase of blood pressure in the systemic as well as in the lesser circuit This is explained in part by an increase of the stroke volume (Cournand Wiggers et al) but an increase of peripheral resistance plays an important role This is mediated according to von Euler and Liljestrand by the oxygen content of the blood acting directly on the arterioles without participation of the autonomic nerves Others assume that anoxia of the carotid sinus and aortic body leads to vasoconstriction in the lesser circuit via axon reflexes (Aviado et al) Little is known about the effect of carbon dioxide retention on pulmonary arterial blood pressure

Since pulmonary infections do cause local anoxia this can result in widespread vascular spasm and an increase of pressure provided it involves large areas of the lung

Even larger pulmonary arteries become narrowed according to von Euler and Liljestrand Thus a local chemical self regulation exists in the lesser circuit which may explain many of the clinical data that defied explanation up to the present The sudden appearance of cardiac failure in a patient with chronic emphysema may be due not only to hypoventilation but also to a sudden rise of pressure because bronchitis with infection causes the formation of mucous bronchiolar obstruction and local hypoxia Actually the old explanation of the cor pulmonale in emphysema was never satisfactory in its assumption of wide spread destruction of capillaries and consequent diminution of the vascular bed Against this was the experience just mentioned that too much of the vascular bed must be destroyed before pressure in the lesser circuit rises Cor pulmonale does not appear if the surgeon removes the right or left lung If we assume that a patient with chronic emphysema develops local anoxia because of bronchitis or local hypoventilation such experiences are now explainable This acute rise of pressure in the lesser circuit causes not only right heart failure but also death

Chronic anoxia and oxygen undersaturation of the arterial blood in the systemic circulation may lead particularly in emphysema with bronchitis or pneumonia to a syndrome of lassitude weakness stupor and coma caused by respiratory acidosis Positive pressure breathing cortisone and the administration of oxygen are helpful but with oxygen administration extreme caution is in order With chronic hypoxia the respiratory centers become insensitive to the stimulus of carbon dioxide and the hypoxia per se regulates breathing If it is abolished by the administration of oxygen respiration becomes too superficial and death results

Carbon dioxide narcosis causes confusion maniacal states drowsiness and coma Headaches and muscular twitching occur (Westlake et al)

Symptoms

There are no characteristic symptoms. Only late, when edema and hepatic enlargement appear, is the attention of the patient and the physician directed to the heart. Usually in the early stages such symptoms as dyspnea and palpitation seem fully explained by the basic pathology in the lungs, the lesser circuit or chest wall. Most of these patients die before the right ventricle fails owing to the underlying disease. This holds not only for patients with emphysema, fibrotic tuberculosis and so forth, but also for those with kyphoscoliosis (respiratory failure).

Anginal Pain. Patients with cor pulmonale have two complaints which are of great interest. *One is pain of an anginal character with typical radiation* into the arms, which may sometimes be relieved by nitroglycerin. This pain occurs in mitral lesions, pulmonary embolism, asthma and emphysema. In one of our patients, a 58 year old man with this type of pain, often excruciating, death occurred in a paroxysm; necropsy revealed rupture of the main stem of the left pulmonary artery, presumably the result of paroxysmal hypertension in the lesser circuit. The rupture extended to the adventitia and was 1½ cm long. An hematoma was found in the pulmonary hilus.

Fainting. *Another complaint is the appearance of effort syncope or tussive* syncope, that is, attacks of fainting during exertion or paroxysms of cough. This event is also seen in congenital heart disease, particularly in primary pulmonary hypertension. The incidence in the latter group was 20 per cent (Dressler). Before fainting the patient experiences dizziness, epigastric fullness, a tight sensation over the heart and choking. The systemic blood pressure falls and sinus bradycardia appears. The patient loses consciousness when the blood pressure reaches a particularly low level. In older literature similar syndromes were known as ictus laryngeus, and in 1876 Charcot described laryngeal vertigo (laryngeal epilepsy). For many years epilepsy was assumed to exist in such cases since tonic clonic convulsions occur during this syncope. One of the explanations available is the assumption of a high intrathoracic pressure during paroxysms of coughing whereby the cardiac inflow and output are diminished to such a degree that fainting occurs. Intrathoracic pressures of 200—300 mm Hg have been measured during violent coughing. Laughter, choking and the Valsalva experiment cause similar fainting. According to McIntosh et al, cough syncope is the consequence of the markedly increased intrathoracic and intraabdominal pressure which is transmitted to the cerebro spinal fluid, so that blood is squeezed out of the cranium. It seems that in certain localities eliciting this type of fainting is a game in which students indulge (Howard et al.). Lethal accidents during this type of fainting have been reported and are said to occur in one to two per cent of the cases. Sudden death in patients with cor pulmonale is known to occur often.

Signs

A regular sinus tachycardia of 100—120 beats per minute is common Arrhythmias are rare While right ventricular hypertrophy is invariable its *existence usually cannot be proven by means of physical examination* because the underlying pulmonary pathology often causes superimposition of the lungs over the heart (emphysema) For the same reason the heart sounds are distant and sometimes scarcely audible The point of maximum intensity of the heart sounds is often near the xiphoid because the whole heart is covered by the lungs Murmurs are more often absent than heard A high pitched diastolic murmur over the pulmonary artery is occasionally audible and derives from a relative pulmonary insufficiency (Graham Steell murmur) A gallop rhythm may be audible over the right ventricle

In view of these difficulties x ray examination is indispensable for diagnosis, although here also difficulties are encountered The form of the heart often cannot be determined in patients with chest deformities (e g kyphosis) and it may be equally hard to judge its size Mitral configuration is common due to displacement and rotation The displacement of the diaphragm likewise makes difficult any estimation of the size and shape of the heart

The section of the right ventricle that is chiefly and in many cases exclusively altered is the outflow tract The axis of this portion of the right ventricle runs almost perpendicular Therefore dilation of the outflow tract leads to prominence of the conus at the left cardiac border and to filling of the cardiac waist One reason for this is the resistance offered by the diaphragm whereby the outflow tract of the right ventricle finds it easier to dilate upward If the diaphragm is low this resistance below is not encountered and enlargement of the conus therefore appears much later if at all (Zdansky) The mitralization is accentuated by rotation of the heart around its axis to the left a typical event in any right ventricular dilatation The hypertrophy and dilatation of the outflow tract of the right ventricle even if considerable do not cause an enlargement of the cardiac shadow in the transverse diameter visible in the posteroanterior view It is easily seen however in the left anterior oblique position

Only late when the inflow tract of the right ventricle also dilates does the transverse diameter of the heart increase to make the heart seem enlarged Since the right ventricle lies mainly in the left chest and in these cases forms a considerable part of the left cardiac border the heart appears enlarged to the left instead of the right even in advanced stages

In pulmonary hypertension a systolic click may be heard over the pulmonary artery explained by the systolic tension of the wall of the pulmonary artery

The systemic blood pressure is often low A systolic blood pressure under 100 mm Hg is not unusual No explanation of this finding is available at present While its occurrence in tuberculosis has been attributed to a toxemia undoubt

edly some other mechanism is at work Spinal fluid pressure is often increased in emphysema and papilledema occurs (Flint)

Clubbing of the fingers and polycythemia are not rare

The electrocardiogram shows right axis deviation and later evidence of *right ventricular strain* *Characteristic changes are found in the P waves* they are very low in lead I and abnormally high but not widened in leads II and III (figure 8b) The reason for these changes and the relation to cor pulmonale is not fully explored at present but the pattern is very common in this syndrome and is typical of it

The pulmonary artery and its main branches are usually dilated Although cyanosis and dyspnea are often present in most cases they are due to the underlying lung pathology The cyanosis is marked and may reach an unusual depth if a secondary pulmonary sclerosis develops or an open foramen ovale exists In advanced stages of pulmonary pathology there is decided anoxemia and often hypercapnia The patient may have an overwhelming desire for sleep Not uncommonly the patient becomes continuously drowsy and may die in semi coma which has lasted for days Convulsions may appear terminally

The liver enlarges slowly and therefore is not tender The edema rarely reaches the degree encountered in the valvular and myocardial diseases These patients usually develop a form of high output failure

Differential Diagnosis

As a rule this is not difficult Clubbing of the fingers and toes marked cyanosis and the presence of a systolic murmur over the heart may suggest a congenital heart lesion in some cases Therefore the distinction is not always as easy as one might guess characteristic murmurs like other pathognomonic signs may be absent in congenital anomalies a secondary emphysema may be found in any cardiac patient A careful examination and evaluation of all findings make possible a correct diagnosis in most cases

The most frequently overlooked cause for chronic cor pulmonale is chronic pulmonary embolization If this picture lasts over many months without pulmonary infarctions and hemoptysis patients develop evidence of congestive heart failure (edema liver enlargement venous congestion) and are treated as instances of coronary disease with failure Anticoagulants or ligation of the vena cava inferior saved lives in several of our patients The diagnosis is missed since the lower extremities need not show any evidence of abnormality the emboli coming from deep thrombi of the legs or from the pelvic veins

Treatment

The therapy is that of the underlying disease Only symptomatic treatment is available for the cor pulmonale syndrome itself Once full decompensation with hepatic enlargement and edema occurs compensation can rarely be re established by therapy

The hypoxemia resulting from the pulmonary disease contributes to this futility of treatment Oxygen under pressure may be life saving In recent years since antibiotic therapy and aerosols have been available considerable help can be given to patients with chronic bronchitis and even to patients with right heart failure — they may become compensated again if careful attention is paid to the treatment of the lung thus abolishing the hypoxia and high pulmonary arterial pressure It has also been pointed out (Moe and Visscher) that the increased load on the right ventricle increases intraventricular tension and that this impairs the blood supply to the right ventricle via the coronary arteries This could also disturb the blood flow through the thebesian veins Moreover increased intra atrial pressure hampers the outflow of blood from the coronary sinus vein

Diamox can be of help in patients with cor pulmonale and retention of carbon dioxide

Sudden death without apparent cause is frequent in these cases as mentioned above Often cardiac decompensation begins insidiously and progresses slowly so that death is the result of the underlying pulmonary disease or secondary infections

In view of the respiratory disturbances so common in these patients breathing exercises with particular reference to the use of the diaphragm are of primary importance in the prolongation of life (Hofbauer Schutz Barach) As mentioned above many of these patients die a pulmonary death (respiratory insufficiency)

While digitalis should be given in the presence of decompensation its results are rarely spectacular unless the other measures mentioned above are used

The injection of morphine is absolutely contraindicated and may lead to sudden death (see last chapter) Demerol is permissible if given cautiously

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Chapter 20

Hypertension

General Remarks

Definition

In one of the first clinical studies on blood pressure von Basch considered a systolic blood pressure of 150 to represent the upper limit of the normal level A diastolic blood pressure of 100 has been considered as the upper normal diastolic blood pressure

A study by the Joint Committee of the Association of Life Insurance Medical Directors of America showed however that values above 140/90 mm Hg are definitely abnormal at any age (Daley et al) The frequently expressed opinion that higher values may be expected in elderly people and that they lack significance is not valid The blood pressure of a normal individual does not necessarily increase with age to a degree that it becomes higher than 140/90 mm Hg Papers with a dissenting opinion appear from time to time but the life expectancy of patients with a blood pressure above 140/90 is decidedly shorter than in those with lower pressures Sometimes particularly in younger subjects there is an elevation only of the diastolic blood pressure the systolic remaining within normal limits The diagnosis of hypertension in such cases is justified

A temporary moderate rise of blood pressure is observed in juveniles An examination of 6000 male university freshmen disclosed a blood pressure in excess of 140 mm Hg in 22 per cent (Alvarez et al) This elevation of the blood pressure in juveniles is best explained by an endocrine imbalance

Significance

Arterial hypertension ranks high among the causes of death more than any other disease it is responsible for cardiac symptoms and signs

Hypertension directly accounts for 15 per cent of deaths in patients over 60 years of age It is estimated that between the ages of 40 and 49 a blood pressure of 150/90 mm Hg or higher occurs in more than one fourth of males and one third of females Fifty per cent of the population over 50 have hyper tension

An increase of the blood pressure with age has been repeatedly reported (Master et al Hamilton et al) but this does not prove that a pressure over 150/90 is not abnormal at any age According to Master in men between the

ages of 50 and 54 the blood pressure may vary between 115/70 and 160/98 normally In men between 60 and 64 it is 190/110

Pickering found the mean systolic and diastolic blood pressures of males between 15 and 19 years old to be 117 2/68 2 while it was 117 2/70 8 in females of the same age Between the ages of 35 and 39 it was 125 2/77 8 and 127 5/79 3 respectively Between 65 and 69 it was 152 1/85 2 in man and 172 9/94 1 in women These figures illustrate the well established fact that with advancing age the incidence of hypertension is greater particularly in women To conclude that a blood pressure of 172/94 in an elderly subject is normal because it is a common finding is in our opinion wrong With increasing age pyorrhea is more common Should we therefore conclude that pyorrhea is normal?

About 140 000 deaths occur annually from hypertension and its consequences in the United States (G Fahr) The great incidence of hypertension in young men examined by the Army draft boards made it the second most common cause for rejection and this has raised questions about the evaluation and prognostic significance of a moderate elevation of blood pressure

TECHNIQUE OF BLOOD PRESSURE DETERMINATION

The blood pressure should always be determined by auscultation and by palpation In view of the many disagreements regarding the correct method for measuring the blood pressure a Committee of the American Heart Association and the Cardiac Society of Great Britain and Ireland made joint recommendations on this subject

The blood pressure should be obtained with the patient lying (British Committee) or seated (American Committee) The arm on which the pressure is taken should be flexed and should be supported at heart level on a smooth surface No constriction of the arm by clothing is permitted The blood pressure may be obtained by an aneroid instrument which must be calibrated annually but a mercurial instrument is more reliable The air vent in the mercurial instrument must not be permitted to clog The mercury at rest should reach exactly the zero mark and in the aneroid instrument the needle should stand exactly at zero The standard cuff *should have a width of 15 cm and should* have a rubber bag 12 to 13 cm in width and 30 cm in length Decompression should proceed at a speed of 2—3 mm per second The cuff should not bulge on inflation and the rubber bag should be applied to the inner side of the arm If possible smaller cuffs should be used for children and wider ones for measuring the blood pressure in the lower extremities The blood pressure should always be taken in both arms Several readings should be taken and the cuff inflated and deflated several times

The systolic blood pressure obtained with the auscultatory method is about 10 points higher than that obtained by the palpatory method It varies at different times of day and is higher after a meal or following excitement The blood pressure may be higher or lower in the right arm than in the left Differences between

the right and left arms are found in 76 per cent of normal subjects Usually the blood pressure is higher on the right side In 8 per cent of normal people the blood pressure was 20—30 mm Hg higher in the right arm (Amsterdam and Amsterdam) Greater differences are due to syphilitic changes at the mouths of the large arteries originating from the aorta to mechanical compression by a cervical rib to the scalenus anticus syndrome or to the pulseless disease Arteriosclerotic changes are rarely etiologic

The level of the diastolic blood pressure is the point at which the sounds suddenly become muffled and dull In cases of aortic insufficiency and other conditions with a large pulse amplitude the exact estimation of the diastolic blood pressure may become impossible The values obtained usually are too low According to Gallavardin the determination of the exact diastolic blood pressure is impossible in about 10 per cent of the cases

When the readings of the systolic pressure by the auscultatory and palpatory method differ widely the Committee recommends accepting the palpatory reading as more nearly correct

In arrhythmias particularly in atrial fibrillation the estimation of the systolic blood pressure is difficult and it is almost impossible to obtain correct values for the diastolic blood pressure

In hyperactive hearts the pulse wave may strike the cuff with such force that sounds are audible distal from the cuff in the cubital artery and too high values of the blood pressure are obtained by the auscultatory method

With small arms and the use of standard cuffs the values of the systolic blood pressure are usually too low With large arms they are usually too high

Like the temperature the blood pressure in normal subjects varies constantly It is lowest during sleep and in the morning Transient rises are often forerunners of persistent hypertension

Auscultatory Gap

A very important but little known source of error in the determination of the blood pressure with the auscultatory method is the so called silent zone or auscultatory gap

With gradual deflation the sounds or murmurs (in the second phase of Korotkow) suddenly disappear and with continued deflation they reappear and permit the estimation of the diastolic blood pressure One may find for example that the sounds appear at 200 mm Hg vanish at 180 then reappear at 130 and disappear completely at 100 The blood pressure of this patient is 200/100 but between 180 and 130 no sounds or murmurs are audible over the cubital artery If the cuff had been accidentally inflated only to 160 and then the pressure slowly released sounds would have appeared at 130 and disappeared at 100 so that the blood pressure would have been considered 130/100 mm Hg Serious errors are avoided if the systolic blood pressure is always determined by the palpatory method as well as by auscultation The auscultatory gap is more

distinct or may appear only when the cuff is held under pressure for some time (Pines and Scherf)

That the level of the venous pressure has some importance for the occurrence of this phenomenon is revealed by another experiment The gap may be found if the blood pressure is obtained with the arm hanging down and disappears if the arm is elevated (Berry) It may exist only in the right or only in the left arm In some patients it is transient while in others it is observed for weeks The auscultatory gap has been found in 10 per cent of hypertensives (Amsterdam and Amsterdam) Apart from those with hypertension it is frequently encountered in connection with stenosis of the aortic valve (Gallavardin and Tixier) It occurs however in nonhypertensives and also in the absence of aortic valve lesions

In some cases of hypertension and particularly when the cuff remains inflated for a while auscultatory phenomena above the gap disappear completely or are present only for a few millimeters so that the physician who deflates the cuff quickly overlooks this phase completely

Cold Pressor Test

The cold pressor test recommended by Hines serves to find an abnormal response of the blood pressure to an external stimulus At first the basal blood pressure is measured with the patient resting in the supine position for 20 to 60 minutes While the cuff is still on one arm the opposite hand is immersed in ice water (4° Celsius) up to the wrist and the blood pressure is again measured 30 to 60 seconds later The higher reading is recorded as the response The hand is then removed from the ice water and the blood pressure is taken every two minutes until it returns to the basal level No vasodilator or sedative drugs are permitted for 24 hours before the test

Elevation above the basal level of more than 20 mm Hg of the systolic pressure and more than 15 mm Hg of the diastolic pressure indicates a hyper reactor Such a hyper reactor is in greater danger of developing hypertension than normoreactors In normoreactors the blood pressure values return to normal within two minutes after the hand is removed from ice water This is delayed in hypertensives or in patients who are hyper reactors Pickering denies the clinical value of this test

TYPES OF HYPERTENSION

The blood pressure may be increased in a great variety of conditions some of which were mentioned in previous chapters The cause of the abnormal blood pressure is known in approximately 5 per cent of patients with hypertension In the remaining 95 per cent the blood pressure is high without any visible cause or known reason This type of hypertension is called essential hypertension a common but extremely unsatisfactory term that reveals actually an ignorance of the etiology It is probable that the group of patients to whom this phrase is applied will decrease steadily in coming years

Theoretically hypertension may appear (1) with changes of cardiac dynamics (increased contractility) (2) with changes of conditions of the large vessels (aorta) (3) with increased volume of circulating blood (4) with increased viscosity of the blood (polycythemia) or (5) with a narrowing of the peripheral vessels (arterioles) We shall see that instances exemplifying most of these mechanisms are known but that the last mentioned narrowing of the arterioles is present in an overwhelming number of cases

Hypertension is known to occur in certain endocrine disorders in certain disturbances of cardiac action in nervous disorders and in renal diseases and some affections of the urinary passages

1 Hypertension in Endocrine Disorders

Hypo ovarianism The most common cause of hypertension in this group the natural or artificial menopause has been discussed earlier Peference was made to the markedly fluctuating and in later stages even fixed hypertension in women with disturbed estrogen formation it is not a lack of estrogen but the endocrine imbalance in connection with it that seems to elevate the blood pressure in these cases The syndrome of hypertension and tachycardia in women between the ages of 40 and 50 years certainly is often due to this imbalance We have mentioned earlier that many authors consider hypertension in women of this age group as coincidental but this does not concur in our experience

Adrenals Primary aldosteronism with adrenocortical hyperplasia hypo kalemia and hypernatremia causes hypertension The frequency and patho genesis of this complication is not clear (Conn Chalmers et al) Patients with potassium losing nephritis seem to belong in this group According to Genest hypertensive patients secrete larger amounts of aldosterone than normals In primary aldosteronism in addition to the hypertension hypokalemia alkalosis and a tendency to hypernatremia exists Attacks of muscular weakness (inter mittent paralysis) are presumably due to the hypokalemia Diarrhea is common

Enteramine Serotonin These hormones secreted by the argentophile cells of the large intestines play an important but not yet fully analyzed part in the genesis of hypertension While the effect of 5 hydroxytryptamine on the blood pressure is erratic tryptamine without the hydroxy group causes hypertension The 5 hydroxytryptamine seems to regulate vascular tone and constricts the afferent glomerular blood vessels (Erspamer)

Pheochromocytoma

PATHOLOGY While this lesion was occasionally observed by pathologists no clinical description was available until 1922 The lesion consists of a usually benign rarely bilateral tumor composed of mature chromaffin cells of the adrenal medulla or other chromaffin bodies The new growth is encapsulated and may be malignant functioning metastases occur The tumor may weigh a few grams or as much as three kilograms and may also occur in the chest or cranium

INCIDENCE The tumors occur with equal frequency in both sexes and may develop in several members of the same family Poth et al saw them in two sisters and one brother They are most common in younger individuals

SYMPTOMS AND SIGNS In many patients the symptoms are typical The complaints consist of sudden attacks of palpitation with tremor dizziness and chest pain Anginal pain is present in almost 50 per cent of the patients during an attack of hypertension Severe headache and epigastric pain are also common Nausea is often present The systolic blood pressure may rise from 110 to 300 or more and the diastolic from 60 to 140 or more Often with the rise of blood pressure bradycardia or arrhythmias develop Glycosuria and albuminuria frequently develop during an attack Circumoral pallor and pallor of the cold and mottled extremities may be found although in many patients the face is flushed

The diagnosis is often possible on the basis of the history One of the most common complaints is a very severe definitely pathologic headache There may be also abdominal pain particularly in the epigastrium so that an acute abdomen may be simulated There is tingling in the hands and feet occasionally violent palpitation with strong pulsation of the vessels in the neck and anxiety Vomiting blurring of vision or even amaurosis appear The skin is often cold and covered with perspiration after the attack great fatigue and lassitude may occur Pulmonary edema may appear causing collapse and even death in some patients it produces a complaint of a sinking sensation Patients may develop a cerebral vascular accident during the attack

Permanent hypertension may be found without a history of attacks The incidence of this picture is not definitely known for statistical data vary According to Organ it is responsible for 0 47 per cent of hypertension Other authors considering only patients in whom tumors were found give a much higher incidence This syndrome should be particularly suspected when there is hypertension glycosuria and a marked increase of the basal metabolic rate One should bear in mind that hypertension of any etiology persisting for a time may become permanent either experimentally or clinically

The hypermotility of the heart resembles that seen in hyperthyroidism The differential diagnosis from the latter condition is often difficult since these patients often have a markedly increased basal metabolic rate Like hyperthyroidism patients of this kind also have an intolerance to heat slight glycosuria after a prolonged attack may cause the physician to diagnose diabetes In prolonged attacks the temperature is increased The electrocardiogram during the attack may show marked abnormalities of the T waves ventricular extrasystoles and even tachycardias Sometimes the attacks cause so little distress that the patient does not seek medical advice other times the episodes are so incapacitating that medical counsel is a necessity

Since the investigations of Goldenberg and his associates were published it is now established that not only epinephrine but also norepinephrine (in some tumors only this substance) are excreted by the tumor into the circulation

In patients with large tumors bending forward suffices to expel these compounds into the circulation and to provoke an attack This secretion of noradrenaline causes changes in the potassium content of the blood which in turn may be responsible for the cardiac arrhythmias observed during the attack The clinical symptoms and signs vary since in some patients more epinephrine while in others more norepinephrine is secreted

The attacks may last for minutes or hours They may occur at any moment but they are prone to develop at a fixed time often at night Years months or hours may pass between single crises Sometimes it may be possible to provoke an attack by pressure on a palpable tumor which is most often situated on the right side squatting exposure to cold or excitement may also provoke an attack Attacks may appear after exercise Sometimes there is a time relation to the previous meal or excitement

LABORATORY TESTS In addition to the old diagnostic tests — intravenous pyelography and perirenal or better presacral air insufflation now improved by the replacement of air by oxygen laminography and the like — new tests are available Occasionally they may lead to false positive results but in general they are reliable and facilitate the diagnosis False positive results are obtained most often when one tries to provoke an attack by an intravenous injection of 0 025—0 05 mg of histamine In the presence of a pheochromocytoma this causes a marked rise of blood pressure in a few minutes The histamine test may be used when the resting blood pressure is not over 150/110 False negative tests do occur A rise of systolic blood pressure by 60 mm Hg or more and of the diastolic by 30 mm Hg or more is significant

Goldenberg s benzodioxane test is performed by the intravenous injection of 10—15 mg of this substance for the regitine (phentol amine) test 5 mg of regitine are used These substances counteracting the action of epinephrine and norepinephrine cause a definite fall of pressure in a few minutes after the injection in all subjects who have a blood pressure elevation due to pheochromo cytoma False positive tests appear after sedation with barbiturates and Rau wolfia drugs and in uremia At the present time it is assumed that regitine causes fewer side effects than benzodioxane and should be preferred for the test In patients with hypertension in the absence of a pheochromocytoma benzo dioxane may cause a marked rise of pressure (Fremont)

At present the excessive urinary excretion of catechol amines determined by photometric methods seems to be the most reliable test A 24 hour specimen is assayed

Operative procedure of any type particularly removal of the pheochro mocytoma may cause shock Postoperative patients require careful super vision Metastases may be functionally active

Cushing s Syndrome Hypertension appears in the adrenal cortical syndrome which is characterized by marked obesity particularly of the abdomen hir sutism purplish striae hyperglycemia and osteoporosis This syndrome formerly attributed to basophilic adenoma of the anterior hypophysis (Cushing s

spaces in which blood could potentially be stored) are not available in patients with generalized edema because the edema compresses peripheral veins The circulating blood volume being markedly augmented leads to an overfilling of the large veins and an increased cardiac filling and to an increase of the systolic and diastolic blood pressure With a marked diuresis (often following only *one* injection of a mercurial diuretic) the peripheral blood depots become available blood is again stored the amount of circulating blood decreases and the blood pressure falls (Goldhammer et al)

It is not always possible to restore compensation fully and therefore this hypertension may not be reversible and the blood pressure may remain high despite therapy

Since patients with congestion of the kidneys may show marked albuminuria and casts in the urine mistakes in diagnosis are common It should therefore always be remembered that hypertension occurs in congestive heart failure and is often the consequence of decompensation it does not always mean a renal or vascular disorder

3 Hypertension in Nervous Disorders

The influence of the central nervous system on blood pressure was widely discussed at one time but had been somewhat neglected until recently In the last few years this question has again attracted considerable attention (Raab) particularly since the discovery of the carotid sinus reflexes demonstrated the importance of a nervous regulatory mechanism for the blood pressure level

This form of hypertension is accompanied by an increase of rate The increase in cardiac output is claimed to be the chief reason for the hypertension

An increase of intracranial pressure may lead to hypertension most probably because the intracranial vessels are compressed and the centers rendered anemic Prolonged hypertension can be produced experimentally by the injection of kaolin into the subarachnoid space (Dixon and Heller) when it spreads to the cerebral ventricles and by experimental creation of cerebral ischemia Clinically hypertension is observed in brain tumors and in vascular disease causing cerebral ischemia

Hypertension also results when all four moderator nerves (right and left carotid sinus nerves and right and left aortic depressor nerves) are severed this is due to the disturbance of homeostasis and the release of vasoconstrictor centers which are normally inhibited

Cases of encephalitis bulbar poliomyelitis and concussion of the brain and trauma to the midbrain with paroxysmal hypertension have been observed

The importance of fear anxiety and apprehension in the causation of hypertension is also well known This increase of blood pressure stems from the release of adrenalin and noradrenalin and stimuli running from the emotional to the vasoconstrictor centers The importance of these factors in the development of essential hypertension will be discussed later

The Hypertensive Diencephalic Syndrome This form of hypertension described by Page is most often found in middle aged women Such subjects exhibit great emotional instability blush in spots and show red patches on the neck and chest The extremities are cold pale and clammy The neck vessels pulsate strongly The blood pressure is labile and may temporarily reach high values The heart is normal in size and shape for many years and the electro cardiogram does not show any change demonstrating that the blood pressure is not fixed and often reaches normal levels The syndrome resembles attacks seen in connection with organic diseases of the hypothalamus An increased response to 0 25 ml of a standard histamine acid phosphate solution was described in this condition Dermography is common

4 Hypertension in Renal Disease and in Diseases of the Urinary Passages

The occurrence of hypertension in renal disorders is so common that an increase of blood pressure has been considered by some authorities of the past (and is considered even today) to mean an involvement of the kidneys

Humoral Mechanism The mechanism of increased blood pressure appears to have been greatly clarified by recent investigations but is however much more complicated than it seemed at first It must be stressed that the mechanism of hypertension of renal di eases is still unknown there is no proof that a humoral mechanism is responsible

A humoral mechanism in the production of hypertension was suggested by Tigerstedt and Bergmann who isolated a pressor substance from the kidneys Although confirmed these experiments rarely received correct evaluation until Goldblatt demonstrated that constriction of the renal arteries in dogs under certain conditions causes persistent hypertension This hypertension may lead to renal changes identical to those seen in human malignant hypertension The kidney whose artery is clamped does not show these changes indicating that they are secondary to the hypertension Complete sympathectomy does not prevent this hypertension nor is normal blood pressure restored by the operation if hypertension existed (Freeman and Page) Removal of both adrenals causes the blood pressure to return to a normal level (Goldblatt) It was su pected (Hartwich) and later demonstrated that the ischemic kidney releases a sub stance identical with rennin Rennin is an enzyme that unites with blood globulins to form a peptide hypertensin or angiotonin Rennin is probably formed by the cells of the proximal convoluted tubules Another enzyme is present in blood and ti sues (hypertensinase) which quickly destroys hypertensin The normal kidney is able to counteract the pressor effect of the pressor substance formed by an ischemic kidney

Deamination According to others the pressor amines formed during normal metabolic processes are not deaminized by the ischemic (anoxic) kidney and these circulating amines cause hypertension

Kidney Diseases In acute and chronic nephritis pyelonephritis periarteritis nodosa and polycystic kidney hypertension is common but not obligatory so

long as no nitrogen retention exists The reason for the hypertension is unknown Even the hypertension in coarction of the aorta has been explained by a diminution of renal blood supply

It has long been known that hypertension appears in obstruction of the urinary passages and may disappear if the obstruction is removed Hypertension occurs in prostatic hypertrophy in hydronephrosis and in ureteral stone A diminished renal blood supply due to attenuation of the renal vessels is produced by stretch and compression in such cases

Hypertension appears in unilateral compression of the main renal artery by a tumor glands or an abnormality of the vessel It appears in unilateral pyelonephritis or renal embolism In many instances of unilateral kidney pathology removal of the affected kidney abolished the existing hypertension (Howard) As might be expected these operations are not always successful since experimental studies show that a hypertension persisting for a long time leads to secondary vascular changes in the other kidney therefore the hypertension is maintained even if the initiating factor is abolished There is a greater probability of a fall of blood pressure following nephrectomy in these cases if the hypertension is less than two years old Poutasse et al report on hypertension caused by bilateral stenosis of the renal arteries in three patients fourteen fifteen and twenty five years old In one of these patients homografting of both renal arteries abolished the hypertension According to Schaffer and Markowitz nephrectomy in patients with unilateral kidney disease brings a cure in ⅓ of the patients and does not cause any improvement in another third

Despite the fact that urologic hypertension is not common a careful history must be taken and intravenous pyelography should be performed in *every* patient with hypertension of unknown etiology (negative family history) in order to rule out kidney pathology If this is done urologic hypertension will be discovered in patients whose history and physical examination arouses no suspicion of the presence of this condition

The fact that dorso lumbar sympathectomy may diminish hypertension markedly in patients with renal diseases is not compatible with the assumption of a purely humoral mechanism in these cases

Eclampsia (and pre eclampsia) This combination of edema (gain in weight!) hypertension and albuminuria with convulsions coma and death has an unexplained pathogenesis Pennin has however been found in the blood Hyperadrenalism was considered possible Toxemia of pregnancy — a term still in use today even if somewhat out of order and ineccurate — appears more readily in patients with renal disease The syndrome appears in primiparas in the seventh and eighth month but if hypertension already existed it appears earlier more frequently and is more severe Headache nausea and drowsiness often precede eclampsia These attacks like attacks of hypertensive encephalopathy are elicited by the high blood pressure (Byrom)

Sometimes hypertension does not increase during pregnancy but this is not common

Kimmelstiel Wilson Syndrome This syndrome is found in diabetics It consists of albuminuria retinopathy a nephrotic type of edema hypertension — and later azotemia Some of these signs are missing at times The diabetes is often mild The syndrome may also be found in juvenile diabetics It appears after the diabetes is present for 8 to 10 years Death usually occurs in 6 or 7 years A characteristic finding is the presence of hyaline deposits in the glomeruli The urine shows double refractory lipoid droplets There is no specific therapy The mechanism of the hypertension is unknown

ESSENTIAL HYPERTENSION

Definition

As pointed out before essential idiopathic hypertension is diagnosed when all known causes of hypertension are excluded Since the introduction of pyelography with contrast media cases of hypertension are discovered to result from otherwise unsuspected kidney pathology Progress in endocrinology has helped to explain other instances of hypertension All these and the other types of hypertension mentioned however represent the exceptional case — about 95 per cent of patients under 50 years of age with an increased blood pressure belong to the essential type It is undetermined whether we are confronted with a disease entity and it is hoped that more types of hypertension with known mechanisms will be separated from this large group Until the different forms are recognizable we are in favor of retaining this useful term

Inconsistencies in the concept of essential hypertension were pointed out by Raab (1955) According to Pickering (1955) essential hypertension represents the upper end of the distribution curve of blood pressures observed in our population Essential hypertension is not qualitatively different from normal pressure Patients with a blood pressure higher than an arbitrarily selected level are separated as a group with essential hypertension

Incidence

Sex Age Essential hypertension seems to be slightly more common in women than in men Possibly the figures would be different if all hypertensions due to previous toxemia of pregnancy and to the menopause were excluded It occurs at all ages It has been described in a two year old boy in whom it caused progressive heart failure It is not rarely encountered in juveniles or adolescents with essential hypertension in their families particularly with both mother and father suffering from the disease The temporary moderate increase of blood pressure in juveniles which has been mentioned earlier must be kept in mind

The great incidence of hypertension of all types in the general population was discussed above The figures given are also important for evaluating the incidence of essential hypertension if the relation of this form to other types of high blood pressure is remembered

Race It seems established that Negroes living in Africa and Chinese in China rarely have hypertension although they do develop it in the United States with the same frequency seen in the white population (Schwab and Schulze) This difference is significant for it shows that it is not the race but the mode of living and perhaps the type of food which is important

Heredity The frequent occurrence of essential hypertension in several members of the same family is established Essential hypertension is inherited as a dominant characteristic In families whose members have an absolutely normal blood pressure the incidence of an elevated arterial pressure in the offspring is 3 1 per cent If one of the parents has hypertension the incidence rises to 28 3 per cent and in families in which both parents are so affected the incidence is 45 5 per cent In securing the family history it does not suffice to ask whether hypertension or heart disease have occurred in close relatives Since most of the patients do not know that a stroke dropsy angina pectoris or cardiac failure are often consequences of hypertension they answer in the negative For this reason it is better to seek the actual causes of death in the previous generation

It seems that the increase of blood pressure is observed in a progressively younger age group with each generation of a hypertensive family

Constitution The role of constitutional factors has often been discussed Males suffering from hypertension often present the sthenic habitus they are short stocky individuals with a short thick neck and a deep chest On the other hand females often appear frail Exceptions to this rule are however not uncommon Patients of both sexes are frequently obese and diabetes is common in their families

Pathology

In early stages of the disease no abnormal findings are discovered in spite of complete postmortem examination Previous reports dealt with single cases because patients do not often die from this disease at an early stage These observations were confirmed by many biopsies obtained during sympathectomy for the treatment of essential hypertension Hypertension antedates the renal vascular changes (Castleman and Smithwick) In 28 per cent of the cases in which a surgical procedure seemed necessary no changes or only insignificant ones were found in the kidneys

With longer duration of the hypertension the number of patients with abnormal vascular findings increases in persistent hypertension arteriolosclerosis is a more regular finding The kidneys show an irregular granular surface and are contracted There is a focal arteriolosclerotic atrophy with hyalinization of the glomeruli and atrophy of the tubules Similar arteriolosclerotic changes are seen in the spleen liver heart and pancreas

Whether arteriolar sclerosis is a necessary sequel in every hypertension has not been established beyond doubt It does not occur in cases of coarctation of the aorta or in experimental neurogenic hypertension

Etiology and Pathophysiology

The mechanism underlying the development of hypertension of the essential type is unknown It is possible that many factors contribute and that there is more than one etiologic agent

A small minority of physicians still believes that *humoral mechanisms* are responsible But hypertensin has not been found in the blood even in the renal vein of hypertensives it was found only in eclampsia and in hypertensive crises There is no proof that other pressor amines are responsible This holds in particular for norepinephrine which more than any other substance when injected intravenously imitates the clinical picture of essential hypertension since the cardiac output and cardiac rate is not increased Actually only one pressor substance has been found increased namely pherentasin (Schroeder) which has been isolated from the arterial blood of hypertensives Its importance as a responsible agent is undecided The same holds for the vasoexcitor material (VEM) discovered by Shorr and his collaborators *It has been isolated in humans and is found in* increased amounts in hypertensives Its composition is unknown It is formed in the kidney under anoxic ischemic conditions Simultaneously vasodepressor *material (VDM) which has been recognized to be the protein ferritin is formed in* the liver Like renin — from which VEM can be differentiated — it does not cause hypertension directly but is said to sensitize the vessels to epinephrine

During the administration of desoxycorticosterone ACTH and cortisone hypertension may occur Abnormal adrenal function may be responsible in other unknown ways In this connection the occurrence of hypertension in aldosteronism *is of interest*

Selye considers hypertension to be a disease of adaptation During stress large amounts of corticotropic and corticoid hormones are discharged Stress *may cause hypertension and renal changes similar to nephrosclerosis An excessive* adaptation mechanism is said to lead to the clinical picture of hypertension The hypertension in Cushing s syndrome the necessity of the function of the adrenal glands for the maintenance of experimental hypertension and the hypotension of Addison s disease show the importance of the adrenals Details cannot be evaluated as yet

According to some authors the kidney maintains a normal blood pressure by inhibiting extrarenal pressor mechanisms Nephrectomy therefore increases the blood pressure This extrarenal pressure mechanism may be located in the adrenal cortex

According to Volhard hypertension is caused by a decreased distensibility of the aorta and carotid arteries leading to an excitation of the receptors of the depressor nerves with higher pressure levels A similar mechanism is discussed by Kedzi *who found the excitability of the receptors of the depressor nerves and the* depressor reflex to be normal Nervous tension causes a rise of blood pressure which in turn produces less stimulation of the pressure regulating nerves in those *with a hereditary tendency to degenerative processes in the arterial wall and*

changes of the elastic fibers Heymans also considers a decrease of tonus and resistance to stretch of the supra aortic arterial wall as the primary mechanism of hypertension

It seems certain that *nerve tension* causes a rise of blood pressure Thus Graham found 187 subjects with hypertension among 685 soldiers in an armored brigade during the last war who had experienced at least one year of desert warfare with great excitement and stress The mean blood pressure was 178/114 mm Hg In 38 per cent a systolic blood pressure of 160 or more was found and in 26 9 per cent the diastolic pressure was 100 or over Out of 33 patients with hypertension the pressure returned to normal in 28 within two months after the excitement ceased

In the Texas City Disaster in 1947 Ruskin found hypertension in 103 out of 180 patients examined Injury of the hypothalamus causes hypertension hypertension was provoked in rats by audiogenic stimuli (Medoff and Bongiovanni)

The frequency of nervous hypertension (anxiety hypertension) is indicated by its presence in 14 per cent of 1574 applicants at a military procurement office

The fact that many emotions great mental strain, rage and anxiety cause a temporary hypertension is further evidence of the role of a nervous mechanism in the development of essential hypertension A hyperexcitable sympathetic system an abnormal vascular response to physiologic stimuli or an abnormality of the vasomotor centers (Raab) may be responsible Spinal anesthesia may cause a fall of blood pressure to almost normal levels in hypertension

The incidence of persistent hypertension seems greater in those who have had a transitory elevation of blood pressure in their youth

A certain type of personality is said to be common in patients with hypertension Such patients are very active great planners very dynamic and quick in every action They talk fast and give an excellent history They undress quickly for examination eat rapidly never walk but run One must concede however that at times patients with essential hypertension belong to the quiet slow deliberate type and seem exactly the opposite to the patients just described

Certain other personal traits have been found to be common There is great perfectionism and a subnormal assertiveness Emotional instability and compulsive tendencies exist There is often maladjustment Schroeder considers essential hypertension to be a psychosomatic disease

A combination of several of the above mentioned mechanisms is possible and even probable

An abnormal or individually exaggerated response of the autonomic nervous system to the normal excitements of daily life leads to a temporary slight narrowing of the peripheral arterioles and to transient hypertension Narrowing of the vessels in the central nervous system may prolong and accentuate this hypertension since the reduction of the cerebral blood supply causes chronic hypertension Constriction of the renal vessels and stimulation of the adrenal cortex accentuates and prolongs the bouts of hypertension by the formation of pressor substances and production of pressor hormones A vicious cycle develops (Wilson and Byrom)

Thus the following formula may be real nerve stimuli act on the hypothalamus which in turn increases the tonus of the sympathetic system This leads to renal ischemia and to greater peripheral resistance because of vasoconstriction which is in part humoral Sooner or later there are anatomic vascular changes in the arterioles since this part of the circulatory system offering the chief resistance is subject to the greatest stress in hypertension it causes a drop of blood pressure from the high level in the arteries to the low one in the capillaries

Symptoms

In most of these cases hypertension even when marked causes no symptoms whatever The increased blood pressure is discovered accidentally on the occasion of a life insurance examination or a similar situation Many patients aware of a high blood pressure for many years deny any discomfort Understandably many patients particularly the more sensitive and alert type develop symptoms from the time they are informed of the existence of a hypertension They have symptoms because they *know* that they have hypertension Patients are known to have had a systolic blood pressure of around 200 mm Hg for more than 20 years without any complaints

Fatigue Some patients seek help because of increased irritability sleeplessness and fatigue The last mentioned symptom is not rare but its mechanism is unexplained This fatigue is very distressing and is unrelieved by rest The same symptom is also common in arteriosclerosis We are not aware of any simple reliable therapeutic agent for its relief Fortunately the fatigue which plagues many patients may disappear spontaneously for some time but sooner or later it reappears It often occurs without any evidence of cardiac failure

Irritability and Tenseness Many patients are tense they feel driven and despite an effort to do things more slowly and with less expenditure of energy they are unable to put the brakes on This makes one believe that the great irritability and restlessness are not the cause of hypertension but a feature of its clinical picture

Epistaxis Vertigo Occasionally epistaxis is of sufficient severity to necessitate hospitalization It is explained by changes in the capillaries of the nasal mucosa Tinnitus and attacks of vertigo are not rare Vertigo occurs on change of posture and is sometimes so severe that the patient is unable to lift his head from the pillow or to change position in bed

Headache This is one of the most common symptoms Often it is present on awakening or early in the morning and vanishes after an hour or more It may be occipital or frontal and tends to be symmetrical rather than unilateral It may have a migrainous character Strong pulsations of the meningeal arteries are probably responsible In most cases there is no parallelism between the height of the blood pressure and the severity of the headache Sometimes however the headache is decidedly more severe when the blood pressure rises and therapy which lowers arterial pressure abolishes the headache In malignant hypertension the headache may be due to cerebral edema and then is relieved by lumbar puncture Nausea

and vomiting may occur Sudden appearance of exceedingly severe headache is ominous

Loss of Weight In advanced stages of hypertension especially in patients with generalized arteriosclerosis a sudden inexplicable loss of weight often impels the patient to seek medical advice While it is generally believed that hypertension is more common in the obese the idea is by no means unanimous (Proger) However undernutrition as it existed during the siege of Leningrad in the last war does cause a fall of pressure In patients with hypertension obesity may aggravate the cardiac burden In patients without hypertension or cardiac disease a syndrome has been described consisting of obesity alveolar hypoventilation arterial hypoxemia with secondary polycythemia and pulmonary hypertension causing right heart failure Reduction of weight causes marked improvement (Kerr and Lagen Weil)

Other Complaints In the late stages when such complications as cardiac failure coronary atherosclerosis angina pectoris or cerebral vascular sclerosis develop the symptoms peculiar to these disorders appear

Pounding and palpitation on effort or at rest are common complaints With the onset of left ventricular failure nocturnal dyspnea and cough begin

Signs

Blood Pressure The chief sign is elevated blood pressure The blood pressure should be taken repeatedly with the patient in the recumbent position and the highest as well as the lowest values should be recorded The auscultatory values should be checked against those obtained by palpation and estimation should be made in both arms

If hypertension is found the physician should try to obtain the reading with the patient relaxed — for example after a good night s rest or after the administration of a barbiturate (0 2 Gm of sodium amytal) or a similar sedative

In essential hypertension the systolic and diastolic blood pressure are both elevated The value of the diastolic pressure is more important than that of the systolic Every value above 95—100 is very suggestive The systolic level may exceed 300 mm Hg and the diastolic may be higher than 180 but usually the systolic pressure is near 200 and the diastolic near 100 mm Hg

Palpation Physical examination starts with palpation of the peripheral arteries Hypertonus of the vessels may make the pulse scarcely palpable despite the hypertension With medial calcification the vessels assume a pipestem character

Palpation of the chest and the precordial area in particular reveals no characteristic signs in benign hypertension Marked hypermotility is palpated in malignant hypertension this may be due to the activity of pressor substances

Percussion and X ray Examination The heart may be of normal size and shape for many years It has been correctly pointed out (Raab) that hypertrophy and dilatation do not parallel the height of the blood pressure Other perhaps hormonal factors may play a role The left ventricle responds to increased aortic pressure with greater residual filling and therefore higher initial tension of the

muscle fibers causing secondary hypertrophy These changes involve the outflow tract of the left ventricle and cause downward displacement of the apex without enlargement of the transverse diameter Since the lower part of the elongated ventricle is hidden in the abdominal shadow negative x ray findings particularly with films taken in the postero anterior view in a patient known to have hyper tension for many years are not rare In the course of the disease sometimes even



FIG 86 Aortic configuration of the heart and widened aorta in a 50 year old patient with hypertension

20 years after the onset the left ventricle also dilates in a transverse diameter and an aortic configuration appears (figure 86) Cardiac hypertrophy and dilatation may assume great proportions and with the exception of patients with aortic insufficiency the hypertensive heart may be the largest and heaviest encountered If the patient has a cor bovinum but no aortic insufficiency or hypertension it is probable that he once had hypertension which has since vanished

The development of pulmonary congestion coincides with the mitralization of the heart

The aorta is *dilated in the early stages* but it is a dynamic dilatation which is not demonstrable at necropsy Later with the appearance of atheromatosis

the dilatation becomes permanent This dilatation is diffuse but in the ascending aorta it fails to reach the degree usually seen in aortitis The descending aorta is also dilated in contrast to the situation usually observed in aortitis

The elongation of the aorta sometimes causes a pulsation that is palpable in the jugular notch The elongation also displaces the right subclavian and the innominate arteries upward in the neck so that abnormally strong pulsations may be found on the right side of the neck above the clavicles which may be mistaken for those of an aneurysm The upward displacement of the aorta and innominate artery shortens the distance between the orifices of the right carotid artery at the innominate and its entrance into the skull This leads to an abnormal course and even kinking of the right carotid (Brown and Rowntree) A similar kink may also produce an aneurysm like pulsating mass in the left side of the neck when the elongated sclerotic left carotid artery pursues an abnormal course (Parkinson et al)

Auscultation The heart rate is usually normal or slightly increased The first heart sound is accentuated at the apex and the second sound is abnormally loud over the aorta This accentuation is absent however in many cases even if obesity or emphysema the usual reasons for the absence of the second sound are not present The second aortic sound was found normal in 46 per cent of hypertensives (Cossio et al) With the increased fibrosis and the appearance of lime salt deposits in the aorta the second sound may assume a metallic, ringing character

A systolic murmur is often audible over the apex and the aorta Sometimes both murmurs originate in the aortic area and the systolic apical murmur is merely transmitted In patients with emphysema the aortic murmur may disappear when the aorta is covered by lung in this instance the murmur is audible only at the apex

Most often the aortic murmur is due to dilatation of the left ventricle and the widening of the aorta in the absence of dilatation of the aortic orifice a relative stenosis mechanism exists Later especially in elderly patients sclerosis of the aortic valves may be responsible The apical murmur may also be created by sclerosis of the mitral valve particularly its aortic leaflet Naturally both of these murmurs the result of valvular sclerosis also occur in elderly patients without *hypertension The murmur due to atheromatosis* is often mid systolic and accordingly is easily separated from the first heart sound

With the development of a more pronounced dilatation of the left ventricle a relative mitral insufficiency appears and with it a new loud blowing systolic murmur may be heard at the apex

Gallop rhythm and pulsus alternans are common findings in hypertensive patients with the onset of myocardial failure

A diastolic aortic murmur due to a relative aortic insufficiency is in our opinion extremely rare

Fundus Examination Examination of the fundi shows many abnormalities This examination has fundamental significance in establishing the degree of

vascular changes It should be done frequently to watch the progress of alterations The earliest change consists in a contraction (narrowing) of the arteries but often even this is missed in early stages so that the fundi are considered normal With the development of arteriosclerotic changes new phenomena appear The vessels become tortuous the light reflex is wider copper or silver wire patterns occur the lumen of the arteries becomes irregular and venous compression is visible at crossings

Hyaline deposits in the narrowed arterial walls cause the silver wire appearance Even in the early stage acute constriction of the arterioles may lead to exudates (cotton wool patches) and hemorrhages these disappear readily when vasospasm (acute angiopastic retinopathy) relaxes All atherosclerotic changes are occasionally found without elevation of the blood pressure

With the development of very marked vasoconstriction and higher spinal fluid pressure the optic disc swells and papilledema appears

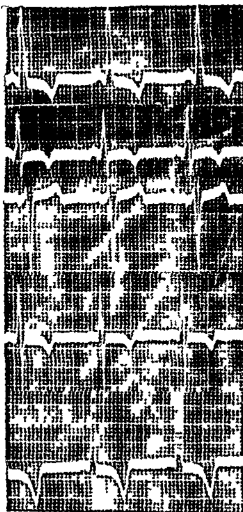


Fig 87 Pattern of left ventricular strain in a 58 year old woman with hypertension

Importance of Retinal Findings There have been repeated endeavors to differentiate several stages or grades of the disease One method is based upon the retinal findings (Wagener and Keith) In the first grade the retinal findings are normal This large group embraces those who have a normal blood pressure at rest and during sleep moreover they have few symptoms or signs In the second grade some evidence of retinal vascular sclerosis is present but none of hemorrhages or exudates In the third grade mild vasospastic retinopathy with hemorrhages and exudates exists but no papilledema In the fourth grade because of an increased spinal fluid pressure papilledema is present in addition to the other changes This hypertensive neuroretinopathy is always symmetrical While this differentiation of the retinal changes is a great aid in evaluating the

status of the patient the prognosis depends upon many factors such as the status of the heart and brain

Leg Ulcers Ischemic ulcers of the legs are rare but do occur in hypertension (Martorell) they develop in the lateral supramalleolar region For the most part they appear in women between 50 and 70 who have had hypertension for many years Intimal proliferation is found in the arteries There is no specific therapy and the ulcers are slow to heal

Laboratory Findings In many cases the urine shows no albumin but in others albuminuria is very pronounced from the start Granular and hyaline casts also appear Sometimes the albuminuria is due to congestive heart failure

Examination of the blood urea nonprotein nitrogen and creatinin shows normal findings until there is destruction of the kidney parenchyma and renal ischemia The cholesterol level of the blood is occasionally slightly elevated The basal metabolic rate is frequently abnormal and even excessively high without any demonstrable thyroid involvement or existing cardiac failure

Electrocardiogram The electrocardiogram shows often left axis deviation this is however common in healthy subjects In late stages with the development of left ventricular hypertrophy and dilatation the RS T segment and T waves are displaced below the zero line in lead I (and often in lead II) while they are displaced upward in lead III This pattern of left ventricular strain is the same as that seen in aortic insufficiency (figure 87) The chest leads reveal more diagnostic changes In V2 leads the R waves may be absent and the S is deep in V5 there is a tall R wave, rarely followed by an S and the RS T as well as the T are depressed below the isoelectric line

In many cases of hypertension particularly in the advanced type with hypermotility of the heart a very short P R interval is found (Scherf) Thus in figure 87 in addition to the pattern of left ventricular strain a P R interval of 0 12 is present The conduction time often is even shorter This tracing was obtained from a 58 year old woman with a blood pressure of 210/120 mm Hg This shortening of the P R interval is by no means characteristic It is common in thiamin deficiency

Course

The tempo of the disease is subject to great variation Progress may be slow and a patient seen ten years after the first examination may still show the same findings At other times the course is stormy and the changes progress rapidly

Importance of Fixation of Blood Pressure From a purely clinical standpoint for many years two stages have been differentiated in patients with essential hypertension The first is the stage of fluctuating blood pressure values The examining physician finds a systolic blood pressure of 200 mm Hg in the first measurement If the determination is repeated in a few minutes after the patient has become adjusted and quiet the systolic blood pressure may be 160 mm Hg In this stage any excitement mental or physical exertion causes

a remarkable rise of blood pressure The innumerable impressions of daily life furnish sufficient occasion for maintaining the hypertension continually during the day During sleep or after the administration of sedatives after prolonged rest in bed the blood pressure is normal

After a variable period the stage of fixed blood pressure is reached Additional rise from excitement still occurs but neither sleep nor sedatives reduce the blood pressure to a normal level

By this time arteriolosclerosis may develop and the clinical picture as well as the course complications and prognosis depend on the degree of vascular changes in the different organs Circulatory complications are the most common renal complications are rare

Circulatory Complications These are manifold At least 50 per cent of the cases develop heart failure The progressive coronary sclerosis damages the myocardium which works under the heavy strain imposed by the hypertension this soon results in congestive heart failure In many patients, coronary sclerosis leads to angina pectoris on effort and myocardial infarction as the consequence of coronary occlusion It was noted earlier that hypertension is a common finding in patients with exertional angina and coronary thrombosis A small percentage of patients show evidence of obstructive atherosclerosis of the peripheral vessels of the lower extremities The early appearance of vascular complications does not depend on the height of the arterial blood pressure

The electrocardiogram may be very helpful in evaluating the progress of coronary sclerosis In addition to the left ventricular strain mentioned before slurring and widening of the QRS complexes (intraventricular block) and T wave changes may indicate the presence of coronary sclerosis The fact must be stressed however that marked coronary sclerosis need not cause any electrocardiographic changes under certain circumstances

Cerebral Complications Paralysis hemiplegia aphasia occur in 13 per cent of hypertensive patients In some cases these accidents are due to embolism from mural thrombi in the left ventricle More often they result from arterial thrombosis or hemorrhage or are due to cerebral edema Local vascular spasm (cerebral crises) are responsible for many temporary lesions (Byrom) The same mechanism causes the so called hypertensive encephalopathy

Headache and vertigo often precede cerebral vascular accidents for some time

In all probability cerebral hemorrhage is not the result of a simple rupture of an artery Experiments on cadavers show that a tremendous pressure (1 520 mm Hg) is necessary to rupture a cerebral artery Angiospasm causing local ischemia and therefore damage of vessels or damage of brain tissue seems to be the responsible cause Congenital anomalies are also possible factors

Other Complications Sclerosis of the renal and cerebral vessels may produce or increase an existing hypertension as pointed out earlier

Sclerosis of the splenic or hepatic arteries in this stage does not lead to complications A coexistent nephrosclerosis does not cause complications for

some time because an impairment of renal function can be found only by very sensitive special tests

Not rarely, diabetes appears in *this stage* and is attributed to a sclerosis of the pancreatic arteries *Glycosuria* is found frequently and should be looked for particularly after a meal rich in carbohydrates Nephrosclerosis however increases the renal threshold and may prevent glycosuria despite a markedly elevated blood sugar *The blood sugar level is therefore much more important than the amount of urinary sugar in the appraisal of these cases*

With rapid failure of the heart or following coronary thrombosis with myocardial infarction or because of slowly developing myocardial fibrosis the systolic blood pressure may fall while the diastolic remains at a high level Thus the pulse pressure is reduced markedly In some cases the diastolic blood pressure also falls to a normal level then the diagnosis of a former hypertension is suggested only by the discovery of an unusually large left ventricle We would like to stress again the frequent occurrence of fibrotic occlusion of secondary and tertiary branches of the coronary arteries in middle aged and elderly patients particularly in the presence of hypertension (Baurle Rau) This event receives too little consideration by clinicians

Renal Complications Only a small percentage of patients (7—10 per cent) reach the stage of renal insufficiency and die from uremia This event occurs most often in the group of patients who develop the syndrome of malignant hypertension

MALIGNANT HYPERTENSION

This is not a disease entity but rather a syndrome that appears in different diseases which lead to hypertension — essential hypertension chronic nephritis and pyelonephritis Therefore the term malignant phase or accelerated phase of hypertension seems to be more appropriate The pathogenesis is unknown but it seems to occur when the diastolic blood pressure is very high

Clinically the disease is said to have entered the malignant phase when the course is rapidly downhill when the diastolic blood pressure is elevated to values about 130 *mm Hg* and remains fixed at that level and the fundal changes (mentioned below) appear

Histologically the condition is characterized by the appearance of necrosis of the afferent arterioles in the kidney focal necrosis of the tufts a proliferative response of the glomeruli and diffuse endarteritis (proliferative capsulitis)

Malignant hypertension often appears in relatively young people In one series 67 per cent of patients were between 35 and 55 years of age one subject was only 17 (Ellis)

In principle the symptoms are those of essential hypertension but more accentuated *Headache* is common and progressive Papilledema and retinal hemorrhages are rarely missed The higher diastolic pressure causes a higher spinal fluid pressure leading to papilledema However Perera found papilledema when the blood pressure was low Renal function is impaired the specific

gravity becomes fixed and the blood contains an increase of nonprotein nitrogen and creatinine Albuminuria may be missed for some time but red blood cells appear in the urine early The differentiation from chronic nephritis is very difficult The outlook is always very bad and the disease runs a downhill course ending within a few years Death may occur within one year after symptoms appear

One of the best clinical signs is the elevation of the diastolic blood pressure to values above 130 even values of 160—180 are observed The marked narrowing of the arterioles responsible for this sign leads to renal insufficiency vascular wall necrosis and cerebral edema However the accelerated phase does not depend on the height of the blood pressure (Perera) It may occur even when the blood pressure is considerably lowered by cardiac accidents Palpation often shows a marked hypermotility of the heart as in hyperthyroidism and the whole precordium may pulsate The P R interval in the electrocardiogram is often shortened and unusual values of less than 12 hundredths of a second often are observed The serum of patients with renal insufficiency contains cardiotoxic substances which may be responsible (Raab)

The picture of malignant hypertension can be produced experimentally by the Goldblatt mechanism but not by neurogenic factors

In general the prognosis is very poor but spontaneous improvements do occur Fortunately improvement is more common with modern therapeutic measures The average survival time in the group observed by Schottstaedt and Sokolow was 8 5 months The two year mortality was reduced from 90 to 50 per cent by sympathectomy and currently is even lower with hexamethonium and apresoline The rice diet alone or any diet containing 20 grams of protein daily may abolish this syndrome and the azotemia may disappear with it Page found that therapy with pyrogens may be successful The patient receives bacterial pyrogens intravenously daily for one month so that the temperature is raised to about 38 Celsius after each injection

Prognosis

The prognosis of essential hypertension is difficult to ascertain since even a very mild form may suddenly assume a malignant course particularly in young people moreover complications like coronary thrombosis may appear unexpectedly and change the whole picture The mode of life the habits of the patient in regard to the quantity of food taken alcoholism and the like are important in the ultimate prognosis The prognosis also depends upon the sex of the patient women having in general a better prognosis

If patients have electrocardiographic changes indicative of myocardial damage and usually caused by coronary sclerosis or if gallop rhythm exists or if attacks of cardiac asthma have appeared the prognosis is dubious An elevation of the diastolic blood pressure above 120 mm Hg is significant — this may lead to progressive changes On the other hand patients may have a diastolic blood pressure of 130 mm Hg for years without developing evidence of the malig

nant phase Observations are on record in which a blood pressure of 220/120 was observed for 20 years or 225/140 for 16 years (Perera) and milder forms of hypertension for 50 years (Pratt) Women in particular sometimes tolerate excessive blood pressure well for many years The average duration of hypertension according to Perera is 19 years The height of the blood pressure is not the only factor important for the prognosis nor for the size of the heart or the changes in the electrocardiogram An improvement of the fundus or the disappearance of hypertrophy patterns in the electrocardiogram have been observed without change of blood pressure Burgess stressed the chances of a normal or nearly normal life expectancy in patients over 50 with hypertension in the absence of cardiac cerebral or renal damage

Therapy

In discussing the therapy of essential hypertension it is necessary to stress from the beginning that no rational therapy is available because we lack knowledge of the developmental mechanism of this condition Great progress has been made in symptomatic management however and therapeutic nihilism is unjustified

Five types of therapeutic measures will be discussed (1) general measures (2) diet (3) drugs (4) surgery and (5) symptomatic treatment

General Management The attitude of the physician when hypertension is found has primary importance Unfortunately too many physicians still frown and look very serious when they find a hypertension Advice is often given which convinces the patient that the situation is extremely grave Actually the patient must be told that the blood pressure is elevated, for without this information certain measures that require his cooperation are impossible On the other hand the exact readings need not be given despite the possibility that some patients will go from one physician to another until one is found who will unhesitatingly reveal the height of the blood pressure The patient attaches too much importance to the different levels of pressure found on different occasions a rise of 5 mm for example may mean impending disaster to him

After discovery of the hypertension it is advisable to do a general examination including (in advanced stages) tests of renal function (of which Volhard's concentration test or a modification thereof is still the most reliable) a roentgen examination of the chest an electrocardiogram and an intravenous pyelography If all these findings are negative it is important to stress that it is possible for the patient to live a symptom free active life and to live for a long time The hypertension need not cause complaints for 30 years It is important to stress that there is no danger of a stroke (the complication most dreaded by the patient) and that while there is need for continuous medical observation frequent visits are not required The patient should not become blood pressure conscious

A frank discussion of the mode of life should follow Sources of apprehension fear and anxiety should be abolished if possible Excessive mental strain should be avoided as well as physical overwork Excessive responsibilities extracurric

ular activities and emotional conflicts should be avoided If hypertension is discovered in young individuals a profession should be suggested in which mental and physical strain are minimal Rest periods vacations and long sleep at night should be secured The patient must avoid overeating The quantity of food is not less important than the quality The time is past when red meats or meat in general were forbidden Foodstuffs with a high content of fat such as eggs tongue liver cream and all fats are not permitted There is no proof that normal quantities of spices are harmful There is no objection to small quantities of alcohol in early phases but smoking should be forbidden since there are patients in whom the blood pressure always rises after smoking Sex problems must be discussed frankly and any undue excitement or apprehension in this question should be avoided Cystitis and pyelitis if present particularly in women must be treated by specific measures

The blood pressure may fall if obese people reduce their weight therefore a low caloric diet is warranted in such patients

Diet In recent years the diet in patients with hypertension has received increasing attention For years this was neglected and — in spite of the pioneer work of Allen in addition to that of Ambard Strauss and Volhard — was considered to be a peculiarity of Continental Medicine It is to the credit of Kempner that with the publication of his work on the rice diet the attention of physicians was again drawn to the importance of diet in hypertensive patients

At the present time one often sees as usual exaggerations of dietetic therapy Patients with a blood pressure of 150/100 mm Hg are put on a salt free diet and patients with coarctation of the aorta or old people with a purely systolic hypertension from atheroma and loss of elasticity of the ascending aorta are tortured by a strict salt free diet which of course is useless in such patients

A strictly salt free diet that is a diet containing not more than 200 mg of sodium leads to a fall of blood pressure in about 40 per cent of the patients Often it is not tolerated A salt poor diet containing around 500 mg of sodium only rarely helps The salt free diet is built on lanolac baked potatoes sugar and oleomargarine and is gradually amplified with the aid of diet prescriptions such as those made available by the American Heart Association In the first edition of this book we mentioned that the loss of sodium by the body is accelerated by a few injections of a mercurial diuretic but this measure is rarely necessary

RICE DIET On the basis of studies of the metabolism of isolated kidney cells Kempner introduced the rice diet initially only for renal hypertension guided by the idea that it would diminish the load on the kidneys just as the load on the heart is diminished in patients with cardiac damage by the avoidance of exertion Later the diet was employed in other forms of hypertension as well and with results that were startling

The diet consists of 250—300 grams of rice of any type daily with fruits and orange juice It contains about 2000 calories only 5 grams of fat 20 grams of protein daily 200 mg of chloride and 150 mg of sodium One banana daily is permitted avocados nuts and dates are avoided Fluids are given only in the form

of fruit juices and the amount should not exceed 1000 ml daily The rice is boiled or steamed the fruit and juices are fresh and canned ones are permitted only if no sodium salts were used to preserve them

Vitamin A (5000 U) Vitamin D (1000 U) thiamin chloride (5 mg) riboflavin (5 mg) and calcium pantothenate (2 mg) are given daily A little iron should be added After a few months some green (non leguminous) vegetables may be added and later lean meat broiled or boiled Weak coffee is also permissible

During treatment particularly in the first three weeks the serum sodium and urea should be watched because of the possibility of the patient losing large amounts of salt by the kidneys and developing hyponatremia and azotemia If mild azotemia is present it is not a contraindication to the diet

The diet is easy to explain but hard to follow It is monotonous and only a small percentage of patients have the will power to go through with it In those who do success with a considerable fall of blood pressure (in 70 per cent) and of cholesterol (in 40 per cent) will be accomplished The heart becomes markedly smaller the electrocardiogram becomes normalized and abnormal changes in the fundi disappear Headache and palpitation disappear Azotemia diminishes and the patient feels better

The method of action of this diet is not clear At first any effect was denied on the basis of brief observations of only a few patients Actually the diet must be followed for many months (for a year in one of our patients) until some effect is observed In others a fall of blood pressure is seen after four or five days Later investigations — by the Medical Research Council in Great Britain for example — yielded the same result that is a beneficial effect in 70 per cent Even in patients with papilledema astonishing results have been reported (Newborg and Kempner)

In spite of these results and the experiences of others one still finds remarks in the literature that the beneficial effect is obtained because of the fanaticism of the supervisors of the diet their influence on the psyche of the patient and similar effects But no fanaticism could abolish the papilledema of 23 out of 88 cases before the rice diet was introduced

The consensus at the present time apparently is that the diet s efficacy stems from its low content of sodium the chief argument being that patients who experience a fall of pressure during the diet show a rise as soon as salt is added We do not consider this a convincing argument since with other modes of therapy as well addition of salt may cause the pressure to rise The rice diet is poorer in fat and proteins than any other diet and the influence of these factors has had little study An action through the adrenals is one of the possibilities In the first three months the patient is in a negative nitrogen balance but soon particularly because of the protein sparing action of carbohydrates equilibrium is reached It has been stated that the rice diet should not be any better than one of barley or macaroni To this one must answer that rice is a staple food which contains more than any other the necessary amino acids only methionine and histidine are said to be lacking

It is astonishing that even on hot summer days the patients never develop a low salt syndrome provided salt does not leak from the kidneys Appearance of great lassitude headaches apathy anorexia and muscle spasm point to the presence of salt depletion

How long this diet can be continued without harm has not been established as yet

In patients who because of their occupation are not forced to eat in restaurants and who have the will power we consider the rice diet a measure that if followed certainly prolongs life

Here as in the salt free diet half measures are of no use Only strict adherence to the diet brings help It should not be abandoned before strict observance for a year has failed to bring about success

RESINS Resins will be discussed in further detail in the section on diuretics They are of help but are not a substitute for a salt poor diet In patients on a normal diet with reference *to salt resins absorb only a small quantity With* the use of resins certain risks are involved and the question of whether the slight increase of the salt intake possible with their employment helps sufficiently to take the risks and unpleasantness involved must be answered in the negative

In general the resins are disappointing in patients with hypertension In patients with hyperkalemia they may be useful in diminishing the potassium content of the serum and tissues

Drug Treatment Sedatives particularly phenobarbital and chloral hydrate with bromides have great value as an adjuvant to induce relaxation

Almost all of the drugs recommended during the years such as iodides preparations of garlic bismuth subnitrate and many others seem to be useless There is no proof that the frequently used purine derivatives have a beneficial effect We wish to reemphasize however that experimental atherosclerosis caused by cholesterol feeding can be prevented in rabbits by the simultaneous administration of iodine

SULPHOCYANATES Treatment with sodium or potassium sulphocyanate may have an appreciable effect in lowering blood pressure and in relieving head ache Due to their great toxicity however these substances were soon abandoned although treatment involving their use has been revived repeatedly To reduce the incidence of toxic manifestations it has been recommended that the blood level of the thiocyanates be checked frequently

No explanation of the mechanism of the fall of the blood pressure during the administration of potassium thiocyanate is available An action through the adrenal cortex has been assumed

Administration of the drug is contraindicated in patients with kidney lesions because here even a single dose may elevate the blood level for 2 to 3 weeks Severe atherosclerosis cerebral complications congestive heart failure or angina pectoris are also considered contraindications

The single dose is 0 2 Gm The dose for different patients must vary because the individual excretion of the thiocyanates varies greatly Usually three tablets

of 0 2 Gm are given daily for three days and then two a day until a blood level of 8—12 mg per cent is reached The headaches disappear even with a level of 3—6 mg per cent With higher levels toxic manifestations are common They occur however even with lower levels Maintenance may be kept with one tablet a day or 3 to 5 tablets a week Continuous treatment for many months or years has been reported without complications or untoward signs On the other hand early toxic manifestations are frequent and develop in approximately 20 to 30 per cent of those treated fatalities have been reported despite biweekly determination of the blood level which never exceeded 10 mg per cent The plasma level may suddenly rise without apparent cause

The earliest signs of toxicity are weakness and nausea Dizziness hallucinations confusion and other psychotic manifestations with illusions depression convulsions and coma pains in the jaw thrombophlebitis purpura and dermatitis Cheyne Stokes breathing abdominal pain and fever may follow Signs of toxicity may persist for 3 or 4 weeks despite immediate cessation of treatment Often death is not preventable Therefore several observers oppose the general use of these dangerous drugs Our personal experience is in complete agreement with this attitude The blood pressure is appreciably reduced in about 30 to 40 per cent of the cases treated and symptoms such as headache may be greatly relieved But the dangers intrinsic to this method of treatment are great and no proof is available to show that it prolongs life The blood pressure rises soon after treatment is interrupted As with many other drugs the use of which yields occasional success but also dangerous complications many authorities are enthusiastic until they encounter the first fatality despite every precaution In rare cases however with an unusual rise of blood pressure and headache and the impossibility of giving relief by other methods potassium thiocyanate may be tried Its use in hypertensive crises was mentioned earlier It has been recommended (St Pierre) that sodium thiocyanate be injected intravenously in subjects with headache Twenty cubic centimeters of a solution containing 1 396 Gm of sodium thiocyanate is injected This amount does not cause toxic blood levels

Since therapy with thiocyanates diminished the blood pressure decidedly in some cases the question arises whether this reduction is not associated with danger As soon as organic changes develop in the arterioles it is argued hypertension is a necessary compensatory mechanism to insure tissue nutrition If the blood pressure falls less blood is forced through the narrowed vessels into the tissues and their nutrition suffers Urea clearance tests however reveal no diminution of kidney efficiency in hypertensives following marked reduction of blood pressure with thiocyanates On the other hand it is a common observation that a slight reduction of blood pressure following coronary occlusion may be associated with evidence of disturbed cerebral blood supply or an increase of blood nonprotein nitrogen and creatinine these signs promptly disappear when the blood pressure rises again

RAUWOLFIA SERPENTINA This climbing shrub from the foothills of the Himalayas and the Malayan peninsula was known for centuries in India as a

remedy for hysteria some forms of insanity for snake bite and as a vermifuge In recent years Indian physicians first became aware of the beneficial effects observed when this drug was used in hypertensives The crude extract from the root leaves or a purified fraction (alseroxylon) of the plant or a purified alkaloid (reserpine) are used Actually a fall of the blood pressure occurred according to one observer in 60 per cent of patients treated A good effect is obtained from this tranquilizing agent particularly in nervous irritable patients with mild hypertension but remarkable improvement was also observed in malignant hypertension In those patients in whom Rauwolfia preparations do not help the administration of veratrine or Apresoline in addition often brings improvement In rare cases there was an orthostatic hypotension without collapse The blood pressure begins to fall in some individuals after 3 to 12 weeks Following intravenous injections there is a latent period of an hour While originally larger doses were used the Food and Drug Administration now recommends that only the equivalent of 0 25 mg of Serpasil or rescinnamine be administered daily Larger doses may depress the blood pressure more but the side effects increase too much The hypotensive effect may persist after the drug has been discontinued for four weeks

The relative harmlessness of reserpine is illustrated by the following episode a 20 month old boy ingested 260 mg of reserpine (Serpasil) He slept during most of the succeeding twenty four hours his face was flushed and the temperature was 101 4 F There was a tachycardia The sleep was not deep and the child could be awakened at any time for feedings There were no after effects

In patients with rheumatic valvular lesions or coronary sclerosis on the verge of decompensation the appearance of severe edema and hepatic enlargement is noted when Rauwolfia preparations are given

Some of the side effects — which are few — are useful One is bradycardia or at least a reduction of the pulse rate by 10 per cent This seems to be caused by a central inhibition of sympathetic tone Another is the disappearance of constipation Loose bowel movements slight light headedness diminished libido at the beginning of therapy muscle and joint pains bronchitis stuffiness of the nose rarely epistaxis or bloody discharge otitis restlessness anxiety nightmares gain in weight fatigue buzzing in the ears and even Horner s syndrome are observed Diminished activity leads to gain in weight No tolerance develops and the therapy can be continued for years

A more serious and not extremely rare complication especially when larger doses are used is marked mental depression Some authors found mental depression in 10 per cent of their patients treated with the alkaloid reserpine Some report a similar effect on the blood pressure but no mental depression when another alkaloid — rescinnamine — was used The mental depression particularly occurs in patients with depressive tendencies or maladjustment earlier in their lives After cessation of the drug the depression may persist for 4 to 6 weeks Suicidal tendencies agitation and insomnia occur particularly with larger doses

Parkinsonism appears often if larger doses are used Epistaxis diminished mental activity inability to concentrate and impaired judgment have been reported Exacerbation of ulcerative colitis occurs It is still undecided whether peptic ulcer is a contraindication Hemorrhages are observed during medication Gastric hypersecretion is common

It seems that there is a greater fall of the diastolic pressure with the administration of preparations made from the crude root than with reserpine The differences are however small The Rauwolfia alkaloid rescinnamine is as effective as the alkaloid reserpine It causes the same side effects however often with less severity There are patients who exhibit with reserpine on the other hand a lesser degree of some side effects than rescinnamine

Achor et al found nasal stuffiness in 83 per cent of their patients dreaming or nightmares in 42 per cent depressive effects in 17 per cent laxative effects in 28 per cent muscle aches or cramps in 9 per cent dizziness in 6 per cent and urinary urgency in 4 per cent It has been recommended to omit the drug in one week of four when very marked untoward effects appear Since administration of only 0 5 mg of reserpine for two weeks often caused massive gastric hemorrhage or perforation of a gastric ulcer it has been recommended not to give larger doses than 0 25 mg daily Great caution is also indicated in persons with a history of ulcerative colitis

In patients on Rauwolfia therapy undergoing surgery significant hypotension marked bradycardia have been observed during the anesthesia It has therefore been recommended that treatment with these drugs be omitted at least 2 weeks before elective surgery (Coakley et al)

Rauwolfia preparations have the advantage of normalizing the blood pressure and not causing subnormal pressures Many patients experience a pleasant sensation of calmness and well being during the use of these compounds while an exceptional patient must stop using them because of unpleasant side effects particularly increased excitability

The mode of action is for the most part central (hypothalamic) but stuffiness of the nose and other observations point to an action on the autonomic nervous system Interaction between reserpine and serotonin has been reported (Shore et al) Reserpine increases the discharge of metabolites of serotonin which act as antiserotonins It is said to antagonize the blood pressure rise due to serotonin under certain experimental conditions (Schneider and Pinehart) or to displace serotonin in the central nervous system

In most cases 0 25 mg of reserpine daily or 100 mg of the root extract daily suffice Combination of Rauwolfia with chlorpromazine (Thorazine) has been recommended Of the latter drug 15 mg was given three times a day (Fiber) Reserpine given intramuscularly in the amount of 2 5 mg causes a marked predictable hypotensive effect which begins after 3 hours The fall of the blood pressure is smooth In crises 2 5 mg are injected every 12 hours

HYDRALAZINE (APRESOLINE) This phthalazine derivative has a chemical structure that is new in therapy (Bein et al) It is remarkable because it brings

about a fall of blood pressure in 60 per cent of patients but side reactions are seen with relatively small doses in about 70 per cent of those treated Johnson and associates saw the blood pressure fall to normal limits in 42 per cent of their patients It was lowered in an additional 23 per cent Despite the fall of blood pressure the blood flow through the kidneys is increased There is a tachycardia apparently caused by direct stimulation of the heart

The side effects consist of headaches flushing peripheral edema hemorrhages in the gastrointestinal tract palpitation giddiness anorexia hiccups a grippelike syndrome with fever anginal pain (the drug is contraindicated in coronary sclerosis but how can one be sure of its absence?) nasal congestion lacrimation tachycardia skin rashes periorbital edema drowsiness or overstimulation myalgia pancytopenia tingling of the extremities nausea and vomiting

When large doses are given for a while (over 600—800 mg) rheumatoid arthritis and syndromes like those of the collagen diseases appear occasionally a picture similar to the one of lupus erythematosus is observed even with L E cells in the blood There is a rash fever arthritis anemia hematuria an enlargement of spleen and lymph nodes One observer saw this syndrome in 13 out of 139 patients who were treated with doses over 800 mg daily Lee found the lupus erythematosus syndrome in 12 per cent of the patients receiving more than 300 mg of hydralazine daily

One begins with doses of 20 mg four times a day by mouth and gradually raises this amount after 4 to 6 days until a desired effect is obtained or some of the numerous side effects force discontinuance of the therapy Some side effects disappear when an antihistaminic drug and aspirin are given with every dose of hydralazine Many side effects disappear with continued treatment Following an intravenous injection of 2 5 mg the blood pressure falls within a few minutes and returns to the original level after 4 to 8 hours

In many cases another drug capable of lowering blood pressure must be added to obtain success Some patients develop tolerance In some daily doses of even 900 mg have no useful effect

The mode of action of the drug is not established and seems to be complex There is certainly a depressant effect on the vasopressor center and a slight sympathicolytic and adrenolytic action The chief effect is relaxation of smooth muscles Some of the pressor substances (pherentasin) circulating in the blood are inhibited

In hypertensive crises an intravenous injection of 20—40 mg causes a fall of blood pressure for several hours

ERGOT PREPARATIONS Ergotamine tartrate and dihydroergotamine 45 have a peripheral vasoconstrictive action The three compounds dihydroergocrystine dihydroergokryptine and dihydroergocornine given in equal parts (manufactured under the name of Hydergine) lower the blood pressure In acute rises of blood pressure the amount of 0 3 mg given intravenously after dilution with saline causes an appreciable fall of blood pressure but the oral adminis

tration of this adrenergic blocking agent is disappointing although favorable reports have appeared in the literature Mild effects are counterbalanced by resistance which appears early Nasal stuffiness and bradycardia are noted

DIBENAMINE AND RELATED COMPOUNDS Dibenamine belongs to the alkyl amines and is a peripherally acting adrenergic blocking agent It causes severe toxic effects and cannot be given orally it was soon abandoned The slightly modified but similar compound Dibenzyline is given in doses of 20 mg in the form of gelatin capsules Its side effects are gastrointestinal irritation syncope on standing drowsiness nasal stuffiness and weakness Because these side effects exist it is rarely recommended

Priscoline an imidazoline may cause marked rise of blood pressure angina pectoris exacerbation of a peptic ulcer and has been abandoned for the treatment of essential hypertension

VERATRINES Veratrine has been used for almost a century in eclampsia toxemia of pregnancy and hypertensive encephalopathy In recent years some of the alkaloids have been isolated particularly protoveratrine which has the advantage that the dose is regulated according to the weight and not by bioassay

Veratrines (Veriloid for instance in the form of tablets containing 2 or 3 mg each is given 3 to 8 times daily) cause a fall of blood pressure via the Bezold Jarisch reflex that is increasing the centripetal stimuli from cardiac receptors and carotid sinus receptors via vagal nerves leading to lowering of the vasoconstrictor tonus Other preparations are Unitensen and Vergitryl A pronounced bradycardia accompanies the fall of blood pressure If excessive atropine abolishes it Provell maleate or Veralba are purified protoveratrine preparations which can be obtained as tablets of 0 2—0 5 mg Up to 6 mg have been given daily Initially one gives 0 5 mg three times daily

Hoobler et al advise giving 0 50 to 1 5 mg after breakfast orally A dose of 0 25 mg is given at 10 a m and the same dose is repeated after lunch

In acute emergencies (hypertensive crises) protoveratrine has been given intravenously (1 5—1 9 micrograms per kilogram) slowly over a two minute period and later 20 micrograms every ten minutes until an effect is obtained Orally subcutaneously and intramuscularly doses of 0 5—0 75 mg four times a day have been used The substance acts within 30 minutes for 1 to 3 hours In general the individual dose varies so much that with all veratrine preparations the trial and error method must be used Thus one begins with the doses mentioned and gradually increases them The disadvantage of therapy with veratrine lies mostly in the fact that effective doses usually cause gastrointestinal symptoms i e nausea and vomiting The nausea appears in some individuals even with the smallest doses

Other side effects consist of substernal and epigastric oppression lethargy and giddiness palpitation salivation and rhinorrhoea Postural hypotension is usually not observed

METHONIUM COMPOUNDS Penta and hexamethonium are quaternary ammonium compounds with a curare like action and are therefore autonomic

ganglion blocking agents Hexamethonium salts are stronger and hexamethonium chloride is preferred to the bromides and iodides owing to the side effects of these ions The ganglion blocking effect is similar to that of tetraethylammonium chloride which also has been recommended but which has been abandoned Most of the effects caused by blocking sympathetic ganglia are useful because peripheral arteriolar resistance is reduced while blockade of the parasympathetic ganglia causes unpleasant side effects

Hexamethonium is a very potent drug which initially should be given only in a hospital with constant supervision The patient should be informed about its side effects (which are mentioned below) in order that he may obtain help in time and avoid apprehension

With oral administration only about 5 per cent of the hexamethonium administered is absorbed by many individuals and therefore the effect is not satisfactory in the majority of patients unless large doses at least 125 mg are given four times a day at the beginning This dose is increased every 5 or 6 days until the desired effects are obtained Not more than 5 grams are given daily For intravenous administration we recommend not more than 2 5 mg as the first dose since we observed precipitous fall of the blood pressure with the usually recommended amount of 5 mg Patients who are on a salt free diet and those who have had a sympathectomy respond with special speed The doses are varied as necessary according to the response of the patient and must be increased after a while since tolerance is very common and a great handicap In the progress of therapy sometimes the ultimate dose has been ten times as large as the initial and very effective ones The intravenous injection acts within a minute the intramuscular within 5 to 15 minutes and the hypodermic within 30 minutes The effect following subcutaneous injection is maximal after one hour Three to 6 injections a day are given

Success is obtained in about 60 per cent of the patients

The therapy is contraindicated in patients with azotemia glaucoma marked prostatic hypertrophy severe cerebral and coronary sclerosis severe constipation and marked renal damage

Because the autonomic ganglia are blocked to a different degree the side effects vary considerably in different patients Some of the effects deserve careful attention by the physician and require special therapy

One of the first side effects is constipation The patient should not go for more than 48 hours without a bowel movement Paralytic ileus has been reported During constipation larger amounts of the compound are absorbed One gives milk of magnesia at the beginning and cascara later the action of hexamethonium on vagal ganglia is counteracted by compounds like urecholine (urethan or beta methylcholine) given in doses of 5—20 mg daily It is not always effective Five milligrams of pilocarpine nitrate or 15 milligrams of prostigmine bromide 1 to 3 times daily may help

Another great danger is urinary retention which is at times very annoying Complete and irreversible sympathetic paralysis with hypotension has been

observed fortunately it is only rarely that it cannot be corrected with neosynephrine or other pressor amines Disappearance of libido and diminished potency is observed but omission of one dose of the compound often corrects this Because of the curare like action general muscular weakness is often noted One of the most common side effects is the orthostatic hypotension which is seen with this compound more than with any other It appears particularly after a heavy meal consumption of alcohol and in hot weather (the patients cannot sweat) Often the blood pressure in the supine position must be kept at a higher level than desirable in order to avoid marked fall when the patient is erect Blurring of vision due to paresis of accommodation is common Interstitial pneumonia has been seen particularly in azotemia (Golden and Bronk) Pulmonary edema and fibrosis develop causing death from asphyxiation (Viersma) Some patients complain of dryness of the mouth due to decreased salivation Otitis media may be seen because of dryness of the Eustachian tube A greater incidence of dissecting aneurysm in hypertensives treated with methonium or pentolinium has been reported

As with Rauwolfia congestive cardiac failure may develop Permanent bilateral blindness following a fall of blood pressure from 246/136 to 180/110 mm Hg in a 34 year old woman has been described (Bruce)

Because of the danger of severe orthostatic hypotension it is important to determine the blood pressure with the patient standing

PENTAPYRROLIDINE (PENTOLINIUM TARTRATE) Pentolinium (Ansolysen) is a synthetic ganglion blocking agent which is apparently superior to hexamethonium and has replaced it It has been estimated to be about five times as strong as hexamethonium and the average duration of its action is longer This claim has been denied by others It is alleged that its action is less variable and the dose necessary to elicit an effect varied between 135—630 mg a day (Freis et al) Some patients need more than 1000 mg per day Side effects are claimed to be less common than with hexamethonium but are the same in nature and strict supervision of the patient especially in regard to the blood pressure in the erect position and bowel movements is equally necessary Heart failure with retention of salt and water caused by therapy with pentapyrrolidine has been described

One gives 10 mg three times a day (every 8 hours) starting one hour before breakfast The dose is increased by 10 mg every second day until dizziness appears in the erect posture The ideal dose is about 20 mg less than that which produces vertigo and fainting The maximal effect appears one to one and a half hours after the administration and lasts for 6 to 8 hours Some authors recommend giving twice the single daytime dose just before bedtime If hypodermic injections are employed one starts with 3 mg three times a day (every 8 hours) The amount is increased if necessary by 0 5 mg every second day

All these ganglion blocking agents are administered at first in the hospital for 3 weeks For the first 5 days it is best to take the standing blood pressure every 20 minutes after each dose omitting only night tests

Heavy meals and alcohol influence absorption An ideal blood pressure is 120 mm Hg systolic this is easily accomplished in the erect patient

Ecolid (chlorisondiamine) is another ganglion blocking agent effective orally and requiring smaller doses It has a longer action than hexamethonium The orthostatic blood pressure must be checked In the study of Grimson the average effective dose varied between 50—100 mg given twice a day This is recommended because of the long action of the drug (12 to 20 hours) One begins with 25 mg per dose Blurring of vision is often disturbing

Inversine hydrochloride (*mecamylamine*) is considered superior as a ganglion blocking agent because it is completely absorbed after oral administration and acts for 6 to 36 hours Inversine is not a quaternary ammonium compound like the other ganglion blocking substances but a secondary amine

One gives initially 2 5 mg once or twice daily by mouth This dose is increased by 2 5 mg every second day until the necessary dose is reached Side effects are very common Seven out of 35 patients who were treated with this substance showed an unusual neuromuscular disorder with tremor anxiety and convulsions (Schneckloth et al) The average dose to which patients respond with a significant fall of blood pressure is 25 to 30 mg Like other similar agents it is given at first only to cooperating patients in hospitals The side effects and dangers are the same as with hexamethonium Psychoses were observed

COMBINATION THERAPY WITH HEXAMETHONIUM AND HYDRALAZINE This method (Hyphex therapy) warmly recommended by Schroeder is said to reduce the blood pressure to normal values in almost 100 per cent of the patients

In the following paragraphs we shall follow the rules elaborated by Schroeder In view of the side effects sometimes dangerous and sometimes very annoying treatment with these two compounds should be started only in a hospital where the patient is observed for at least three weeks Treatment is never started with both drugs simultaneously One should be aware that in severe coronary stenosis with angina pectoris a fall of blood pressure may induce a myocardial infarction Renal function should be satisfactory (phenol red test) Even an encephalogram should be done to rule out a dysrhythmia which with a decided fall of blood pressure may change to a cerebral accident

With the patient seated the blood pressure is taken every four hours day and night

On the first day one starts with the administration of 125 mg of hexamethonium every four hours by mouth If the blood pressure falls to values below 150 mm Hg a dose is omitted Care is taken to ensure bowel movements by means of milk of magnesia or cascara On the second day 250 mg of hexamethonium are given in tablet form every 4 hours with the same precautions and on the third day 375 mg at the same intervals On the fourth the dose is increased to 500 mg every four hours always omitting the dose if the blood pressure falls to below 150 On the fifth day for the first time Apresoline (hydralazine) is given in addition using 25 mg every four hours by mouth On the sixth day the amount of Apresoline is doubled the amount of hexamethonium remaining

the same On the seventh day the dose of Apresoline is increased to 75 mg every four hours By this time the patient usually has side effects and must be persuaded to continue the treatment On the eighth day 100 mg of Apresoline are added to the hexamethonium every four hours If low pressure is attained on one of the preceding days the doses are not increased

It is claimed that with this method a reduction of the blood pressure to normal levels is accomplished in almost every patient After prolonged therapy after the diastolic blood pressure becomes normal the dosage of these drugs can often be diminished (Perry and Schroeder) The same authors had remarkable success in the therapy of malignant hypertension with renal azotemia with the use of ganglionic blockade combined with hydralazine of 46 patients with a nonprotein nitrogen of 30—60 mg per cent 27 were alive and working after almost two years

The effects of the compounds and the accidents caused by the reduction of blood pressure are the same as mentioned above

SUGGESTIONS ON DRUG MANAGEMENT OF HYPERTENSIVES At the present time it is recommended that all patients with hypertension except those with an excessively high systolic blood pressure and with a diastolic above 120 mm Hg be started with Rauwolfia therapy If this method does not bring success within two months we suggest the addition of veratrine or hydralazine For this purpose the mixtures of the latter two drugs which are prepared by the manufacturers are not used Rather veratrine or hydralazine are given in increasing individual amounts ready made tablets do not permit individualization of the treatment

Ganglion blocking agents are necessary only in excessively high systolic and diastolic blood pressures If possible one starts with a Rauwolfia preparation here also and adds Inversin in increasing amounts This is preferable since Rauwolfia in combination with other drugs shows not only an additive but also a synergetic action

A salt poor diet is advised A salt free diet is not recommended since it can rarely be maintained for several years and is of help only in some patients The treatment with the modern drugs makes this impalatable diet unnecessary If the patient who comes for advice already is on a salt free diet there is no reason to tell him to discontinue it

Surgical Therapy At first performed by Pieri for the treatment of hypertension sympathectomy was developed interestingly enough at a time when knowledge of the renal factor in the genesis of hypertension was in the process of investigation and when many clinicians thought that the Goldblatt mechanism was an adequate explanation of the pathogenesis of essential hypertension There is general agreement that the experimental renal hypertension is humoral and is uninfluenced by sympathectomy

The methods of sympathectomy devised are diverse but one fact gradually emerges operations with most extensive severing of the sympathetic system provide the greatest chance for success

A report of 350 cases in which a *supradiaphragmatic* sympathectomy was done (Peet et al) revealed a significant reduction of blood pressure in 51 4 per cent and a relief of major symptoms in 86 1 per cent

With a *subdiaphragmatic* extraperitoneal sympathectomy with resection of the splanchnic nerves a part of the coeliac ganglion and the upper lumbar sympathetic trunk (Allen and Adson) 13 per cent of 224 postoperative cases responded well and 18 per cent to a fair extent In 39 per cent the fall of blood pressure was only temporary and the operative result was poor in 30 per cent There was no mortality

With the *combined approach* that is lumbo dorsal sympathectomy the operation is performed on one side and after about 10 days on the other side Recently both sides have been operated on simultaneously (Smithwick) The sympathetic trunk from the ninth dorsal to the second lumbar ganglion is removed and the great splanchnic nerves are severed

At present sympathectomy is considered to be indicated when the course is progressively downhill when the patient develops papilledema despite medical therapy when the diastolic blood pressure rises to values above 130 in spite of all medical measures when such measures do *not* improve very severe headache and when the mode of living of the patient or his occupation make adherence to the diet or medical therapy under supervision impossible

The operation is not performed in patients beyond 55 or 60 with renal insufficiency (urine concentration not over 1 010 or NPN not below 40) cardiac failure not improved by therapy or very advanced coronary or cerebral vascular sclerosis One should not operate in the presence of an active peptic ulcer

The mortality is 1 to 3 per cent Complications are atelectasis pleural effusion pneumothorax and disturbed ejaculation Operation on a pregnant woman did not prevent normal termination of pregnancy Hospitalization for 4 to 6 weeks is necessary but is appreciably shorter when both sides are operated on at the same session

The prognosis and results of the operation seem better in females With more extensive sympathectomy postural hypotension develops and may persist for weeks and even months The resultant disability is of variable intensity Anhidrosis of the lower extremities develops and ejaculation is lost if the second lumbar ganglion is removed In spite of all these difficulties and handicaps surgical therapy has more to offer in certain patients than any medical measure now available

For the postoperative orthostatic hypotension it is necessary to bandage the legs

The mode of action of the operation is not clear The pooling of blood in the lower part of the body in the erect posture is one of the possible reasons for the fall of blood pressure The operation does not and cannot bring about a cure it can only improve the condition

It is impossible by means of any test to predict the result of the operation in advance In mild cases the success may be meager in advanced cases even

in malignant hypertension the success may be astonishing Unfortunately in many patients the success is only temporary and after a while the blood pressure rises again

Among 275 postoperative patients in the literature Gerbaux noted a very good result in 25 per cent and only moderate improvement in 15 per cent In 28 9 per cent Ray found a normal or almost normal blood pressure postoperatively and in a further 31 6 per cent a significant reduction There was complete failure in 10 per cent According to others good results were seen in 21 per cent but they persisted only in 10 per cent The life expectancy is increased according to Hammarstroem Others have found no change in the lighter milder cases The survival time was increased only in very sick patients Similar results were obtained by Longland and Gibb but better ones by Zintel et al Many of the contradictory results stem from the fact that different methods were employed in selecting patients for operation

A precipitous fall of blood pressure may lead to the appearance of anginal pain and intermittent claudication

UNILATERAL KIDNEY DISEASE The question whether the hypertension disappears following removal of the diseased kidney in unilateral kidney disease has been much debated Since this is not the case in some instances some authors deny the possibility of any cure of hypertension by such a procedure There are however an increasing number of reports in which blood pressure fell when the diseased kidney was removed and particularly in children with hypertension resulting from unilateral pyelonephritis the elevated blood pressure returns to normal following operation (Gasul) In some cases — as in experiments — secondary changes in the other kidney and the entire vascular system preclude a fall of blood pressure even if the obviously damaged kidney is removed

ADRENALECTOMY The newest surgical procedure is adrenalectomy first recommended by Crile and later employed by Wolferth and Thorn and their associates This operation is logical because much work proves the necessity of the adrenals for the maintenance of various forms of experimental hypertension In man if adrenal insufficiency develops hypertension if present disappears and hypotension develops Experimental hypertension does not appear when adrenalectomy has been performed previously Adrenalectomy in man became possible since the adrenocortical hormones became available Thorn et al removed both adrenals completely Wolferth et al reported subtotal adrenalectomy with and without splanchnicectomy Patients should be under 50 years of age without azotemia and without advanced cardiac damage or encephalopathy When cortisone therapy is interrupted patients collapse within 24 to 48 hours In extremely hot weather under various conditions of stress the dose of cortisone (3—60 mg daily) which is often astonishingly small must be increased Sudden death occurs after the operation Even total adrenalectomy does not bring success in some patients! While it is too early to state definitely whether the operation should be performed more often it is certain that it allows many

patients with advanced malignant hypertension to survive and they may recover from a very critical situation

Adrenalectomy is done in uncontrollable hypertension without renal damage when without the operation death can soon be expected Usually the operation is performed in two stages

The measure is still in an experimental stage

Symptomatic Therapy The treatment of the individual symptoms of essential hypertension does not require detailed discussion Cardiac decompensation and angina pectoris are treated in the usual manner If vascular crisis and encephalopathy appear the administration of chloral hydrate and the intravenous injection of hypertonic glucose solution and of magnesium sulfate (20 cc of a 10 per cent solution slowly injected) has been recommended An intravenous injection of protoveratrin is given as rapidly as possible We prefer this compound to Serpasil or hexamethonium

In cerebral vascular accidents the least possible treatment is the most satisfactory one Morphine should be avoided in order not to depress the respiratory centers and not to raise the spinal fluid pressure The value of stellate ganglion block is still under discussion Venesection has the disadvantage of being followed by an additional rise of blood pressure Magnesium sulfate is given for convulsions and cerebral edema

Massage as well as passive and active movement should start early

Despite remarkable results in some cases — the disappearance of papilledema in the malignant syndrome normalization of the blood pressure in a long established hypertension through the rice diet or sympathectomy — there are still those who claim that the game is not worth the candle (Leonard) It is true that often no relief or improvement can be effected as a matter of fact the above mentioned measures have the effect of calling the patient s attention every day to his blood pressure thus making his life truly miserable On the other hand do not patients with diabetes also have to be constantly aware of their illness? And is the result not worth the disadvantages? If future statistics show that treatment initiated sufficiently early stops the further development of the illness that life is prolonged and that complications develop more rarely then a great victory will have been won in the battle against a condition the best advice for which in the past was Take is easy and swallow some phenobarbital

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Chapter 21

Hypotension

NO GENERAL AGREEMENT has been reached regarding the level of the blood pressure at which hypotension may be diagnosed Most observers concur that a systolic blood pressure of 100 mm Hg or less permits the diagnosis of hypotension but some place the upper level at 110

In the new born the systolic blood pressure varies between 50 and 60 mm Hg It gradually rises to values just under 100 mm Hg in children up to the tenth year At puberty the normal blood pressure level for the individuals is reached At this period of life temporary periods of mild hypertension are observed they seem to be caused by an endocrine imbalance

One may distinguish between (1) symptomatic hypotension (2) constitutional permanent hypotension and (3) orthostatic hypotension

Symptomatic Hypotension

This is encountered in the course of various diseases It is common in Addison s disease and in Simmond s hypophyseal cachexia It occurs in shock collapse and during many infectious diseases Hypotension is a common sign of myocardial infarction Pulmonary emphysema bronchial asthma and pulmonary tuberculosis are often associated with a low blood pressure Various forms of neurogenic and hormonal hypotension are discussed by Raab

Permanent Constitutional Hypotension

Incidence This condition was formerly known as essential hypotension and is a common phenomenon It appears in about 3 per cent of otherwise healthy adults Like hypertension it is often familial

Symptoms In a vast number of cases the condition is devoid of symptoms and its discovery is accidental In this instance the physician errs grievously if he informs the patient about the finding Laymen are soon convinced that a serious disease is present and many patients date the beginning of their complaints to the time they were told their blood pressure was too low As a matter of fact this type of hypotension never leads to alarming symptoms it is an anomaly rather than a disease

The associated symptoms are increased lassitude fatiguability palpitation cold clammy hands and feet inability to concentrate and giddiness particularly on any change of posture Patients may suffer from headache and they always

feel chilly The responsibility for all these symptoms in a given case is hard to establish The condition is more common in females than in males

Prognosis The prognosis is excellent Statistics show that the mortality of these individuals is far below that of the general population and the history often reveals longevity in many members of the patient s family

Treatment As a rule medical therapy can be omitted It usually suffices to inform the patient about the nature of his condition its harmlessness and excel lent prognosis Physical exercises massage sponge baths followed by brisk rubbing the application of an abdominal support for patients with enteroptosis and the administration of sedatives for the irritable nervous individual are often helpful A gain in weight is beneficial for these patients but this is extremely difficult to achieve in many instances

It is a mistake to administer drugs in order to elevate the blood pressure Ephedrine paredrine sympathol and adrenocortical extracts have been recom mended and are still prescribed too often With these drugs it is impossible to maintain the blood pressure at a higher level for decades and furthermore this is entirely unnecessary If the patient can learn not to focus attention on the level of the blood pressure the symptoms soon disappear in most cases

Orthostatic Hypotension

In the third group low blood pressure appears transiently on changing from the horizontal to the erect position

Unless certain reflexes were active such change of position always would immediately be followed by syncope In the erect position the vascular bed of the lower part of the body is dilated by increased hydrostatic pressure and plasma is lost by increased filtration pressure Cerebral anemia so called ortho tatic ar terial anemia would appear if certain vasoconstrictive reflexes and an increased heart rate did not act as compensatory and adaptive factors

Therefore under normal conditions when the individual changes from the recumbent to the erect position only minor changes of blood pressure occur The systolic blood pressure falls slightly the diastolic rises a little and the heart beats a little faster

After prolonged recumbency in patients with varicose veins in tabes and in women in the first month of pregnancy this orthostatic hypotension with fainting occurs

In young and healthy individuals vigorous exercise may lead to orthostatic hypotension and even syncope because of pooling of blood in the lower extrem ities

In normal subjects under great nervous tension a temporary 0 diastolic pressure has been observed in the brachial artery while it was normal in the popliteal artery There is usually a tachycardia The phenomenon may last from a few minutes up to an hour and a half

As will be shown in the next chapter the normal adaptive mechanisms are greatly disturbed at times in such a way as to produce syncope when the posture is changed

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Chapter 22

Fainting; Morgagni-Stokes-Adams Attacks

Fainting

Introduction

The functions of the central nervous system and the preservation of consciousness depend upon an adequate blood supply. Accordingly, attacks of syncope are a natural consequence of certain disorders of circulation.

The laity frequently attributes syncopal attacks, whether accompanied by convulsions or not, to organic heart disease. As a matter of fact, fainting and convulsions are more common in cardiac patients than in the general population. Many patients with these symptoms do not, however, suffer from any circulatory disorder.

Formerly, fits (syncope with convulsions) were sharply distinguished from syncope (simple fainting). The latter was considered to lack an aura, to appear only when the patient was erect, and to display no motor phenomena such as twitching or convulsions. At present it is generally agreed that the two conditions merge imperceptibly and the appearance of one or the other is determined only by the degree and duration of the circulatory disturbance.

Syncope accompanied or unaccompanied by convulsions is frequently confused with epilepsy. Mistakes also occur in the other direction, since epilepsy (petit mal) may manifest itself by simple syncope. Some of the circulatory disturbances discussed below may be preceded by an aura and may be accompanied by tonic clonic convulsions and loss of sphincter control. Possible confusion is enhanced by the fact that patients whose attacks originate in circulatory disturbances may present normal findings if a routine examination is done in the interval between attacks. Therefore, it is not astonishing that many patients who suffer from syncope of circulatory origin are referred by the neurologist, sometimes only after considerable delay. The confusion has found expression in the term *epilepsie cardiaque*, which often appears in French literature.

Some types of syncopal attacks — fainting spells of patients with mitral stenosis, especially in those with a ball thrombus in the left atrium, and the fainting observed in patients with aortic stenosis or high pressure in the lesser circuit — were mentioned in previous chapters. The overwhelming agony in coronary occlusion and in aortic dissection may cause syncope. Unconsciousness appears in aortic dissection when it occludes the orifice of the innominate artery

and the left carotid artery Attacks of syncope due to a congenital anomaly of the carotid artery have been described (de Meyer Smith and Hinshaw) Fainting caused by thrombosis of the internal carotid artery or in pulseless disease will be discussed in the chapter on peripheral vascular disease

Vaso Vagal Syncope

Attacks of unconsciousness can occur in patients without circulatory or cardiac disease merely from sudden excitement and emotions Some patients (mostly women) faint whenever they see a funeral procession or at the sight of an open wound or blood An overcrowded or overheated room may cause fainting in others The sight of instruments may make the patient faint in the dentist s office others swoon upon receiving news of vital importance or on witnessing an accident Anxiety fear and pain are responsible

The attacks are particularly prone to occur on recovery from an acute infectious disease and in the course of an acute gastroenteritis They are not unusual in the menstrual period The syndrome is also encountered fairly often in tall rapidly growing individuals especially when they are compelled to stand quiet for a while Occasionally they may even occur when the patient is seated or lying

Pallor appears quickly the patient experiences great weakness and an unpleasant sensation in the epigastrium yawning is common At first the pulse is rapid and almost imperceptible The blood pressure may fall to below 80 mm Hg The patient may be drenched with perspiration On recovery a marked bradycardia sets in which may reach 30 beats per minute or less This bradycardia led to the introduction of the term vaso vagal syncope ' (Lewis) but this expression should not be confused with the vaso vagal attacks described by Gowers In the latter the patients (also for the most part women) do not lose consciousness but are overwhelmed by an inexplicable fear of impending death In the vaso vagal attacks sighing as well as yawning are common and nausea with vomiting are frequently noted Great weakness and headache may persist for hours Some uncertainty or dizziness are premonitory signs The attacks may last for seconds or minutes During the periods of unconsciousness spasmodic movements of the head and arms occur

The mechanism of these attacks is not adequately explained The suggestion that they are of vagal origin (Cotton and Lewis) or are due to abnormal carotid sinus reflexes (Lewis) is not fully substantiated The bradycardia and hypotension seem to develop *after* the onset of unconsciousness and are therefore not initiating factors

The syndrome consisting of the unconsciousness with nausea profuse sweating and bradycardia but otherwise normal findings is readily recognized

Complete assurance of the patient is entirely justified The condition is embarrassing but harmless

Postural Hypotension

This syndrome has special features (Bradbury and Eggleston) and therefore is separated from orthostatic hypotension The systolic and diastolic blood pressure in patients with this disturbance rapidly fall to low levels when the erect position is adopted The attacks are also apt to occur with the beginning of slight exertion such as walking on level ground when the lower part of the body receives more blood

Whereas symptoms usually occur in other types of hypotension when the systolic blood pressure declines to 80 or 90 mm Hg on change of position in this syndrome the systolic blood pressure may fall to 50 mm Hg without the appearance of symptoms There is no nausea sweating or marked change of heart rate Unconsciousness is the sole symptom

It is important that patients with this syndrome usually have some organic nervous disease This happened in the first three observations later this syndrome was described in patients with insufficiency of the anterior lobe of the hypophysis and in those with tabes or bulbar paralysis A similar disturbance was observed in Addison s disease but here the pulse rate increases markedly on standing This syndrome was ascribed to a paralysis of the vasomotor nerves but a central hypothalamic lesion or a peripheral disorder of the sympathetic nervous system leading to a disturbance of the regulating reflexes mentioned above seems more probable Sympathectomy for the treatment of hypertension provokes a similar syndrome

Two patients with postural hypotension had a deficiency in release of norepinephrine and epinephrine (Luft and Euler) Perhaps this was secondary to a lesion of the sympathetic nerves

Bandaging the legs epinephrine paredrine prostigmine methyl sulfate and preparations of the anterior lobe of the hypophysis have been recommended Bandaging and paredrine are more effective than the others

Carotid Sinus Syndrome

It has been known for a long time that pressure at a certain area in the neck may cause syncope The pressure may be exerted manually by a tumor by instruments during an operation or by certain positions of the head This event was clarified by Hering s discovery of the carotid sinus reflexes Several instances of this type of fainting were published and the syndrome received general recognition after the studies of Weiss and his co workers were published

In some individuals increased sensitivity of the receptors in the carotid artery of the central synapses the efferent neurones or an abnormal condition of the effector organ the heart may produce an abnormal effect consisting of syncope following slight mechanical pressure on the carotid sinus In patients with this affection stimulation of the carotid sinus receptors may be evoked by holding the head in certain positions or by turning the head even pressure of the collar may suffice to produce syncope Similar attacks can be readily elicited

by the examining physician when he exerts pressure on the carotid sinus The attack develops after pressure is applied for 4 to 40 seconds on the right or the left carotid sinus Spontaneous attacks last for one half to three minutes and are sometimes preceded by an aura consisting of dizziness epigastric pain or weakness Later pallor appears with loss of consciousness and convulsions which may be generalized The tongue is not bitten and sphincter control is retained Mental confusion hallucinosis and amnesia are common temporary after effects

Analysis of the cardiac and blood pressure phenomena during the syncope led to the separation of three groups of cases (Ferris et al)

(1) Syncope due to cardiac standstill caused by inhibition of impulse formation

(2) Syncope due to an abnormal vascular reaction which causes the blood pressure to fall to an abnormally low level This and the preceding type were anticipated on the basis of facts known about the physiology of the carotid sinus Of great interest however is the third variety the so called cerebral group'

(3) Syncope that appears with normal or almost normal blood pressure and a normal heart rate In this type unconsciousness occurs as early as four seconds after stimulation of the carotid sinus Originally these attacks were ascribed to focal cerebral vasoconstriction but proof to support this conception could not be obtained The existence of an area for the maintenance of the conscious state which can be influenced by reflexes from the carotid sinus was suggested as a possible explanation

An abnormally functioning circle of Willis is probable the cerebral circulation becoming insufficient when one carotid artery is occluded

Denervation of the carotid sinus by operation the infiltration with novocaine or irradiation of a tumor pressing on the carotid sinus may abolish the attacks for a time Recurrences are not rare and it is difficult to explain them after the carotid sinus nerves have been severed

It should be stressed that many patients with the carotid sinus syndrome either have evidence of a myocardial lesion or else are of an age (over 60 years) when such a lesion could be expected This might be anticipated for two reasons

a Vagus effects on the heart i e vagus inhibition are more pronounced in a damaged heart than in a healthy one a fact repeatedly confirmed since Wenckebach s original report Experimental corroboration is easily secured and the event has become thoroughly comprehensible since the chemical mediation of vagal effects was discovered by Loewi A heart already in a poor metabolic state will respond longer and more strongly to released acetylcholine than a normal one

b In many cases however the stronger effect of vagus stimulation is apparent rather than real In the normal heart the higher atrial centers are inhibited by vagal stimulation while the lower ventricular centers are not influenced Therefore these low centers immediately form stimuli if the higher centers are restrained and thus a serious ventricular standstill is prevented Accordingly healthy people have only a slight slowing of the heart rate during carotid sinus pressure

If an electrocardiogram is taken simultaneously it reveals that the sinus node action is completely inhibited and that ventricular centers beyond the reach of the vagus form stimuli for the ventricle In cases of a myocardial lesion however the deeper centers are damaged they do not escape immediately and prolonged cardiac standstill results

It is therefore a mistake to designate every marked effect of carotid pressure as a carotid sinus syndrome and as evidence of hypersensitivity of the receptors in the carotid sinus or hyperexcitability of some other part of the reflex arc Abnormality of ventricular centers may be responsible

Fainting due to Various Other Mechanisms

In another group of patients cardiac standstill results from other nervous reflexes and disorders While these patients have often been considered to have a nervous type of Stokes Adams syndrome in a majority of cases the modern cardiologist would undoubtedly discover an intrinsic heart lesion as the etiologic factor In many reported cases the examination during life and after death was superficial Thus in a case of a seventy two year old man the attacks of unconsciousness were attributed to a bronchogenic carcinoma which enclosed the vagus nerve Electrocardiograms disclosed a sino atrial block and Stokes Adams attacks *due to sino atrial block is a more probable explanation The attacks produced by* reflexes from other parts of the body for instance cardiac standstill on swallowing also belong to this group They have been discussed in a preceding chapter

Morgagni Stokes Adams Syndrome

Nomenclature

The occurrence of epileptiform attacks with a slow (radial) pulse was reported by Morgagni (1761) Adams (1827) and other observers Since the paper of Stokes (1846) on this subject was of major importance and had the greatest influence it has repeatedly been proposed to call the syndrome Stokes Adams attacks

Some authors apply this term only to attacks occurring in patients with heart block Cases of circulatory standstill without block e g paroxysmal tachycardia or ventricular fibrillation must have a separate designation In the present volume the term Morgagni Stokes Adams attacks will apply to all type resulting from a change of cardiac activity regardless whether they are due to cardiac standstill or tachycardia Attacks in which cardiac stand till is not the result of an abnormal intrinsic cardiac mechanism (abnormal carotid sinus reflex or instances of abnormal vagal reflexes) are excluded We deal with a syndrome and not a disease entity

Symptoms and Signs

The syndrome occurs if the cerebral circulation is arrested for a certain period If the standstill of cerebral circulation lasts only a few seconds the patient is unaware of any disturbance It requires an arrest of longer duration at least

6 to 8 seconds to provoke the sensation of darkness in front of the eyes After the standstill lasts for approximately 10 seconds the patient loses consciousness he becomes pale his eyes turn upward and with continued arrest of cerebral blood flow twitching of the arms and legs begins culminating finally in tonic clonic convulsions Urine and stool are evacuated involuntarily An arrest of circulation lasting more than four minutes is often fatal With the resumption of the normal blood supply the face becomes red and a short period of dyspnea develops A respiratory disturbance similar to Cheyne Stokes breathing occurs if one attack quickly follows another

The attack may occur once and never recur or there may be hundreds of them every day If the attacks are brief the patient may be unaware of them and he may continue a conversation from the point reached when fainting occurred After a long attack with convulsions extreme weakness may follow for a few hours Vomiting is not unusual If one attack succeeds another at short intervals the patient may remain semi conscious or somewhat hazy

Mechanism of the Attacks

The syndrome may be produced by two radically different events whose distinction is important with respect to therapy

Ventricular Standstill (*Cardiac Arrest*) In this form there is actual ventricular standstill Various subgroups are known Most frequently ventricular standstill occurs in disturbances of atrioventricular conduction when the atrial stimuli fail to reach the ventricle If the lower centers are normal they immediately start functioning when the conduction of stimuli to the ventricle stops As pointed out earlier however these lower centers are also affected in many patients and a certain time elapses before they can develop their automatic activity The clinical manifestations depend upon the duration of the pre automatic pause or stoppage of the ventricles until the activity of the lower centers begins Therefore in order for this form of Stokes Adams to appear two disturbances are necessary failure of the atrioventricular conduction and failure or retarded development of ventricular automatism

In a majority of patients who develop atrioventricular block the automaticity of the ventricular centers is normal and therefore cardiac arrest appears only in a small percentage of patients with heart block

Since complete heart block is usually transient at first and conduction is temporarily reinstituted only to fail again such attacks often recur If the history of patients with heart block is carefully recorded one notes that for some time the patient has suffered from attacks of vertigo and fainting It may safely be assumed that heart block developed precisely at that time

Rapid Ventricular Activity This form of Morgagni Stokes Adams syndrome formerly regarded as rare but actually common is caused by attacks of tachycardia The faster the cardiac rate the shorter diastole and the smaller the stroke volume If the rate of the heart exceeds a certain limit the period available for cardiac filling becomes too brief and the ventricles expel so little blood

with such feeble force that the circulation for practical purposes is at a standstill or at least is reduced to a minimum With a good cardiac muscle and healthy vessels young people tolerate an extremely rapid ventricular rate even more than 300 per minute very well Older people with sclerotic vessels or patients with myocardial disease or a valvular lesion with predominating stenosis — *the latter resulting in a small stroke* volume from the start — may exhibit disturbances of cerebral circulation with a tachycardia of much lower rate These disturbances may cause temporary vertigo or hemianopsia (Barnes) Prolonged unconsciousness without convulsions may be noted when some cerebral circulation is maintained Hemiparesis which vanishes promptly when the tachycardia *stops is also observed In short the cerebrum like the heart responds to* a tachycardia according to the state of its vessels

Very often the tachycardia evoking this syndrome is due to paroxysmal atrial fibrillation a common event in patients with coronary sclerosis If transient attacks of ventricular fibrillation are not lethal the effect on the circulation is identical with that of complete cardiac standstill Scott and Sancetta observed Morgagni Stokes Adams *attacks caused by ventricular tachycardia in a patient* with A V block they were elicited by mechanical rectal irritation

Syncope d effort (Callavardin) is usually caused by ectopic arrhythmias

Differential Diagnosis

This is difficult for many reasons Examination of the patient between the attacks may not permit a decision in both major varieties Differentiation may be impossible even when the patient is seen in an attack The patient may be pulseless *and may show a cadaveric pallor in complete ventricular standstill* as well as in ventricular fibrillation The heart sounds are often inaudible in patients with rapid ventricular activity or ventricular fibrillation on the other hand rapid rhythmic sounds caused by the contraction of the atria may be audible during ventricular standstill For this reason an electrocardiogram of the patient during the attack *is indispensable in many cases to establish the diagnosis* If the attacks recur at irregular intervals and without warning this may be impossible

Moreover the presence of some irregularity of rhythm between the attacks does not aid in differentiation *One might expect that the first form (ventricular standstill) would occur in patients who exhibit atrioventricular block between* the attacks whereas the presence of extrasystoles would be a sign that the attacks are due to a disturbance of stimulus formation (paroxysmal tachycardia or fibrillation) Recent experience has taught however that the combination *of both forms often occurs and even during the same attack patients may have* ventricular tachycardia or ventricular fibrillation *and complete ventricular* standstill

Three causes are known for such an event The tachycardia may follow standstill because ventricular inactivity leads to an accumulation of metabolites

in the centers this stimulates them and evokes a tachycardia At other times cardiac standstill follows a tachycardia because overactivity fatigues the centers and inhibits their automaticity Finally attacks of ventricular fibrillation and polyfocal ventricular extrasystoles are particularly common in patients with complete heart block presumably because the same lesion usually coronary sclerosis which causes the block also produces irritation of the specific fibers and leads to abnormal stimulus formation A bilateral bundle branch block is often present

Figure 88 was obtained from a patient with coronary sclerosis and complete heart block The patient suffered from typical Stokes Adams attacks with convulsions The electrocardiogram registered repeatedly during the attacks showed that they were due to ventricular fibrillation In figure 88 the complete heart block is interrupted by a group of 13 multiform ventricular extrasystoles Such short attacks often preceded or followed typical ventricular fibrillation in this patient



FIG 88 Complete atrioventricular block and brief ventricular tachycardia with variform ventricular complexes

The differentiation of these attacks from epilepsy hysteria and the attacks of syncope discussed in the preceding section is not always easy Many patients with Stokes Adams syndrome whom we have had an opportunity to see originally consulted a neurologist for epilepsy and some of them were treated for this disease If in the midst of seemingly perfect health a patient suddenly becomes unconscious and has convulsions such an erroneous diagnosis is comprehensible

Prognosis

The outcome depends upon the underlying disease and the mechanism responsible for the attack In a majority of cases the attacks are due to coronary sclerosis We are dealing with a serious complication and sudden death is common *Patients who have these attacks may recover and lead a useful life* for many years with or without complete heart block In one personally observed case in which Stokes Adams attacks followed coronary occlusion hundreds of such attacks appeared daily for many days but the patient was seen alive and well four years later When the attacks are due to ventricular fibrillation the prognosis is much worse than it is in ventricular standstill

Treatment

Therapy should not be started until it has been determined whether the attacks are caused predominately by tachycardia (or fibrillation) or ventricular standstill Treatment without a conclusive diagnosis may result in a serious and even fatal outcome (Scherf) The remedies required in one form possess actions that are *injurious in the other* If cardiac standstill is present stimulants must be given which would be fatal in the tachycardias and in ventricular fibrillation On the other hand depressants like quinidine so effective in the tachycardiac form can induce serious injury if the attacks occur because of standstill Furthermore it seems that quinidine enhances the development of ventricular fibrillation in these cases (Schwartz) Since both types may appear successively in the same patient it is often safer to withhold treatment

In the therapeutic program a distinction should be made between measures indicated in the attack and measures aimed at the prevention of recurrences

Cardiac Standstill If the attacks are due to cardiac standstill and the patient is seen during an episode an immediate attempt to excite ventricular automatism should be made Many times this can be accomplished simply and rapidly by means of sharp blows or slaps to the cardiac area In animal experiments when the heart is exposed a quick blow on the heart with a blunt instrument almost always leads to the desired effect and automaticity starts anew

The intracardiac injection of epinephrine may be lifesaving but often the effect is too violent and there is considerable danger that ventricular fibrillation will replace cardiac standstill For this reason caffeine sodium benzoate is *more worthy of recommendation for intracardiac injection* *Often* pricking of the heart with the needle suffices to awaken automatism For prevention if one attack succeeds another at short intervals epinephrine may be given (0 2 ml of the standard solution) subcutaneously with good results *Ephedrine* in tablets of 30—60 mg three times daily is often useful in preventing attacks caused by ventricular standstill Norepinephrine like epinephrine creates ectopic rhythms and its administration in form of infusions is difficult Isuprel *which can be given in the form of linguets (10 mg) is in our experience a useful* agent (Nathanson and Miller)

Atropine formerly employed without discrimination in all cases of heart block is effective only when the attacks are caused by abnormal vagal reflexes

Barium chloride has also been recommended for the treatment of attacks of cardiac standstill This usage is based on the experimental observation that the compound actually increases the automaticity of the cardiac centers in a very remarkable manner and causes abnormal impulse formation The dose is 40—50 mg of barium chloride that is 20 drops of a 5 per cent solution by mouth three times a day This therapy is not devoid of danger Barium chloride is absorbed from the intestine with great variability in different individuals and the borderline between the effective and the toxic dose is very sharp Accordingly no reaction occurs in some cases until a ventricular tachycardia suddenly appears We do

in the centers this stimulates them and evokes a tachycardia At other times cardiac standstill follows a tachycardia because overactivity fatigues the centers and inhibits their automaticity Finally attacks of ventricular fibrillation and polyfocal ventricular extrasystoles are particularly common in patients with complete heart block presumably because the same lesion usually coronary sclerosis which causes the block also produces irritation of the specific fibers and leads to abnormal stimulus formation A bilateral bundle branch block is often present

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Cardiac Resuscitation In recent years cardiac accidents during anesthesia and surgery have become more common This is partly explained by the increased number of chest and cardiac operations Cardiac standstill occurs when the pleura or the pericardium is opened or when a bronchus or a large blood vessel is ligated In the section on vago vagal reflexes other instances are mentioned Cardiac standstill is observed with increased frequency also because of the pre anesthetic medication used in many institutions in ever increasing amounts Quinidine atropine barbiturates and procaine amide have been recommended They all depress *automaticity of the ventricular centers so that they do not* develop their own rhythm when the higher centers are inhibited The depressed automaticity of the deeper centers is presumably the chief reason that cardiac arrest occurs five times more often in patients with cardiac disease

Ventricular contraction may stop because of intrinsic heart disease or as a consequence of inhibiting vagal reflexes Cardiac standstill has been seen in patients with glosso pharyngeal neuralgia it has been observed during swallowing (Adamson et al)

The same effect (standstill of the circulation) is observed when ventricular fibrillation sets in The treatment is of course very different from that of cardiac standstill

Cooley found it necessary to employ cardiac resuscitation in 48 of 878 patients operated on for pulmonary stenosis Circulation was restored in 33 with normal cardiac action but only 12 survived It is estimated that in 90 per cent of these patients we are dealing with cardiac asystole and in 10 per cent with ventricular fibrillation Others estimate an incidence of cardiac arrest once in 1000—5000 anesthesias (Singleton and DeLoach)

A differentiation between the two forms is possible only with electrocardio gram or inspection of the exposed heart The latter must be employed in practi cally all cases unless the electrocardiogram is observed continuously during surgery as too much valuable time would be lost in setting up and taking the electrocardiogram Heart sounds are heard on auscultation in both conditions because of the continuous activity of the atria

The immediate therapy consists of two measures and is the same in both *conditions first exposure of the heart (if it is not already exposed) to* permit massage second artificial respiration and supplying oxygen which the anesthe tist does best with an intratracheal catheter

The chief principle is the restoration of circulation by massage within 3 min utes Any delay beyond this time may save the patient but the damage to cortical centers may make them vegetating mental cripples with multiple neur ologic manifestations no longer useful members of society In cyanotic or *decompensated patients damage to the centers has been observed* after a stand still of the circulation lasting only 60 seconds

The anatomist Tandler stated in connection with another emergency opera tion that three things are necessary for it courage a sharp knife and some ana tomic knowledge Without regard to asepsis or bleeding a deep cut is made in

the fourth intercostal space and the hand of the physician is forced through it massage of the heart — which is placed between the thumb and other fingers — is started and performed 50 to 60 times a minute The finger readily detects the presence of either cardiac standstill or the characteristic sensation noted when a fibrillating ventricle is massaged the sensation of thousands of worms continuously wriggling Simultaneously 100 per cent oxygen is supplied by a respiratory or tracheal tube or as an emergency by mouth to mouth breathing

In vago vagal standstill the heart often beats immediately after the massage is begun Atropine may be given in small doses Calcium recommended by Blalock has the danger of inducing ventricular fibrillation as has barium suggested by Fauteux Adrenaline also often leads to fibrillation but caffeine sodium benzoate or Isuprel sublingually may be used with advantage

A new method is electric shock treatment (Zoll) which may cause unpleasant burning and twitching of the skin but otherwise is useful

When fibrillation of the ventricles is present the administration of quinidine or Pronestyl has disadvantages since these drugs depress ventricular automaticity so that the end of fibrillation may be followed by standstill The instillation of Pronestyl into the pericardial cavity causes the same effect as an intravenous injection since the compound is absorbed with amazing speed The best success is accomplished with the electrical devices designed for defibrillation An alternating current of 110 –135 volts with a current flow of one or more amperes is used repeatedly for less than 0 5 second Often higher voltage is necessary but it may cause burns Voltage of less than 100 may cause fibrillation Electric countershock applied externally helped 11 times in 4 patients (Zoll)

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Chapter 23

Aortitis

DESCRIBED FOR THE FIRST TIME more than 80 years ago (Welch Dohle) aortitis has been recognized for many years as one of the more common cardio vascular lesions For a long time atherosclerosis which so often accompanies aortitis obscured the diagnosis of the latter even at necropsy Careful histologic examinations disclosed that many museum specimens of atheroma and athero sclerotic aortic regurgitation represented in fact cases of syphilis and syphilitic aortitis

Incidence

Figures concerning the incidence of syphilitic aortitis vary in accordance with many factors the chief of which is the prevalence of syphilis in the communi ty As might be expected the condition is more common in metropolitan areas than in some rural areas More cases will be seen in seaports and in cities with a large colored population The incidence of the disease has been markedly di minished with better treatment of early syphilis and some complications like aortic aneurysm are decidedly less common than they were about 20 years ago as is seen in the following statistical data

In several series of more than one thousand consecutive autopsies before the introduction of penicillin the incidence of aortitis in different parts of the world was found to be 3 6 4 93 6 5 6 89 and 7 per cent

It has been estimated that aortitis was present in 70 to 80 per cent of all syphilitic bodies coming to autopsy However Carter found an incidence of only 22 2 per cent It was estimated that 30 000 to 40 000 persons died each year in the United States from aortitis before the introduction of the antibiotics In untreated syphilis the cardiovascular system was involved in 13 6 per cent of the men and 7 6 per cent of the woman (Clark and Danbelt)

The incidence of syphilitic cardiovascular lesions among patients with organic heart disease has been found in some hospitals to amount to 5 to 15 per cent After arteriosclerosis hypertensive heart disease and rheumatic fever syphilis was the most common etiologic factor for cardiovascular disease

In the colored population its incidence is about three times as great as in the white The lesion occurs in women as often as in men

Pathology

The process begins in the adventitia and media as an endarteritis of the vasa vasorum. It involves chiefly the first 5—8 cm of the ascending aorta and usually but not invariably ends sharply where the descending aorta begins. There is perivascular infiltration with round cells and plasma cells; necrotic areas appear in the media. Primary involvement of the intima is rare. The small necrotic areas weaken the media and may lead to aortic dilatation and the formation of an aneurysm. The inflammatory process in the adventitia leads to adhesions between the ascending aorta and neighboring tissues which permit the diagnosis even before the aorta is opened. The destructive medial process causes intimal depressions which are characteristic in the earlier stages. Later, with the development of fibrosis and secondary lime salt deposits, it is sometimes difficult to make the correct diagnosis without histologic examination.

Adhesions between the lateral parts of the aortic leaflets and the intima of the aorta cause the commissures to widen and the leaflets to separate from each other. This leads to aortic insufficiency. The process in the aorta around the coronary orifices often narrows the ostia and even causes their complete occlusion although the coronary arteries themselves are not involved.

There is no proof that atherosclerosis of the coronary arteries occurs more frequently in patients with syphilitic cardiovascular disease than in others. Arteriolar changes, however, have been described in syphilitic infection (Love and Warner). They consist in thickening of the media and intima. A high incidence of marked peripheral vascular sclerosis in colored patients with aortitis has been noted (Cannon). The formation of a gumma in the myocardium is not common and syphilitic myocarditis is a great rarity.

Symptoms

Aortitis is often described as an asymptomatic disease. As a matter of fact the process often becomes very advanced without the patient having any symptoms. Frequently the lesion is discovered only on the occasion of a routine examination. Heart failure in connection with a syphilitic aortic regurgitation, angina pectoris, syphilitic coronary stenosis, or pressure phenomena due to an aneurysm often provide the first evidence of the disease. With one possible exception, which is discussed below (aortalgia), the symptoms depend upon the complications of aortitis and not on the aortitis itself.

Many patients are surprised by an attack of nocturnal dyspnea or exertional dyspnea. In other instances, peripheral edema and swelling of the liver force the patient to seek medical aid. In a third group the typical anginal pain on effort is the outstanding symptom.

Aortalgia. Still a subject of dispute as a more or less characteristic symptom of aortitis is aortalgia, or aortic pain. Pain of an anginal type may originate in the sensory fibers of the ascending aorta. This explanation seems particularly adequate for the continuous burning sensation behind the sternum occasionally

encountered in cases of aortitis when inflammatory processes exist in the adventitia. This sensation lasts for months and is slightly aggravated by effort. It usually disappears as the lesion progresses, for presumably the sensory nerve fibers are destroyed. We have found this sensation in a small percentage of patients with aortitis, but its existence or the existence of any painful sensation in aortitis without coronary involvement is denied by others (Giertsen, Mattman and Moore).

In cases of aortitis with attacks of paroxysmal nocturnal dyspnea, the complaint of substernal pain at the time of the attack is very common. This complaint is so typical that the suspicion of aortitis is justified in patients who complain of dyspnea and substernal pain at the same time, provided a coronary occlusion can be ruled out. The rise of blood pressure during the attack of paroxysmal dyspnea may in some way be responsible for the simultaneous pain.

Signs

The diagnosis in a typical case is easy because a characteristic syndrome may be present. No sign, however, is pathognomonic and none is invariable. Any single sign occurs only in a certain percentage of cases, so that great difficulties may arise concerning the diagnosis of the lesion and its differentiation from other processes. In many instances the diagnosis is presumptive rather than established.

Abnormal Pulsations. The enlargement of the aorta leads to an increased dullness over the manubrium sterni if the aorta approaches this site over a greater area than normal. The aorta frequently elongates as well as dilates, leading to the appearance of strong pulsations in the jugular notch. The innominate artery now originates higher than normally, the course of the right subclavian artery is higher, and the right carotid artery undergoes some kinking. These pulsations are often confused with aneurysms. They are also found without aortitis if atherosclerosis is present.

Often the closure of the aortic valves is palpable slightly to the right of the sternum in the second or third interspace. This pulsation naturally is found not at the site of the aortic valves but where the ascending aorta approaches the chest wall. While not characteristic of aortitis, this phenomenon otherwise is rarely encountered, since marked aortic dilatation with accentuation of the second aortic sound are necessary for its appearance. It is very rare, therefore, in simple hypertension. If the phenomenon is found in patients under 50 years of age, aortitis should be suspected.

The frequent narrowing of the orifice of the large arteries originating from the ascending aorta (innominate, left carotid, and left subclavian artery) by the syphilitic process leads to marked difference in the pulses of the right and left sides. Complete or almost complete disappearance of one carotid pulse or one brachial pulse with a difference in blood pressure is not rare and also permits the diagnosis. These signs often are mistakenly considered to be evidence of aneurysm. Actually they are common in uncomplicated aortitis.

Percussion In many cases percussion reveals no cardiac enlargement while in others marked dilatation to the right and left with an aortic configuration or mitralization of an aortic heart appears This occurs if hypertension aortic regurgitation or narrowing of the coronary orifices complicates aortitis

Auscultation The second aortic sound is often changed It is accentuated and ringing (tambour like drumlike tympanitic hollow) This change presumably the result of anatomic changes in the aortic wall is not peculiar to aortitis for it may be encountered in patients with atheromatosis of the aorta and hypertension with sclerotic changes of the aortic wall In pure hypertension there is only an accentuation of the second aortic sound without a tympanitic or bell like character If discovered in patients under 50 without hypertension the sign is a very strong argument in favor of the diagnosis of aortitis

Usually a systolic murmur due to eddies caused by the dilatation of the vessel is audible over the aorta Often this systolic murmur is also heard at the apex and should not be confused with a mitral murmur

Blood Pressure The blood pressure is often increased Systolic blood pressure values over 150 are found very often in patients with aortitis (Boyd and Scherf) We would estimate that hypertension is present in about 50 per cent of the fully developed cases in the white race In the colored group the percentage is higher This elevation of blood pressure is interesting since no relation between syphilis and essential hypertension seems to exist The systolic hypertension is usually the consequence of lost elasticity of the ascending aorta The diastolic pressure is also increased in a majority of cases An explanation for the diastolic hypertension in aortitis is still lacking

Other Findings Evidence of neurosyphilis is often found In some observations it was present in 26 per cent of the cases

The serologic reactions are positive in about 80 per cent of cases percentages of positive reactions of 86 per cent (Beckh) and even 92 6 per cent (Carter and Baker) have been reported The spinal fluid is abnormal in almost 50 per cent The treponema immobilization test may be positive when the Wassermann reaction is negative

In youthful patients with severe rapidly progressing aortitis elevation of the temperature to over 38° C has been observed If an aortic regurgitation coexists the erroneous diagnosis of subacute bacterial endocarditis is often made

The erythrocyte sedimentation rate is often accelerated but this finding is rarely of diagnostic value

Frequently in aortitis — as in aneurysm — sensitivity to percussion is elicited over the spinous processes of the second to fourth thoracic vertebrae

Roentgen Examination and Fluoroscopy These examinations greatly aid in the diagnosis One of the earliest signs is a dilatation of the ascending aorta particularly in its first portion Prominence of the aortic arc at the upper right cardiac border if found in a person under 40 years of age without a high diaphragm or coarctation is a very suggestive and helpful finding Dilatation of the

aorta may however be absent or may be missed since the supravalvular part of the vessel is hidden in the cardiac shadow

It is important to stress that even in patients with fully developed aortitis or syphilitic aortic insufficiency evidence of aortic dilatation and elongation is not necessarily present if the process involves only the portion of the aorta situated around the valves and the orifices of the coronary artery without spreading upward

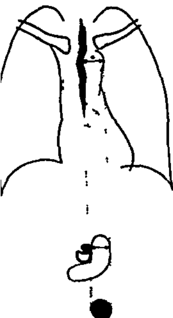


FIG 89



FIG 90

FIG 89 Measurement of the diameter of the arch of the aorta by the Kreuzfuchs method (Zdansky)

FIG 90 Calcification of the ascending aorta and aortic arch in a patient with syphilitic aortitis

The diagnosis of an aortic dilatation should never be based on measurements of the vascular band in the postero anterior projection Examination in the oblique positions is necessary and very informative Unfortunately exact measurements of the width of the aorta in its different portions is not possible The most reliable method is that of Kreuzfuchs by which the width of the part of the aortic arc forming the aortic knob can be estimated This method is based on the fact that one part of the aortic arc takes a purely sagittal course and lies close to the esophagus even causing a light impression on it with a displacement from left to right (figure 89) This indentation is easily seen if a contrast medium of barium is swallowed by the patient First the point of the aortic knob which

is the farthest to the left during systole is found and marked orthodiagraphically on the screen then the deepest point of the "aortic bed" of the esophagus is found while the patient swallows the barium

The diameter of the healthy aorta ascertained in this way is 1 8—2 5 cm Patients over 60 years of age may have values up to 3 cm Some authors recommend the deduction of 2—3 mm for the thickness of the esophageal wall periesophageal connective tissue mediastinal pleura and the double thickness of the aortic wall Since all these values are relatively constant it has been proposed that the deduction be omitted

In addition to the aortic dilatation the discovery of lime salt deposits in the aortic knob is common (figure 90) The frequent appearance of these calcified placques in aortitis is ascribed to the great incidence of secondary calcification in the involved tissue of the aortic wall The appearance of this sign in patients under 50 years of age is also a strong argument in favor of the diagnosis of aortitis

Angiocardiography In some instances this has revealed an irregularity of the lumen variations of thickness of the wall of the aorta and tortuosity

Electrocardiogram While the electrocardiogram furnishes no diagnostic help it is significant for prognosis since it aids in establishing the diagnosis of a complicating coronary stenosis The discovery of a simple left axis deviation or of a normal electrocardiogram may indicate a healthy myocardium while in many patients with few complaints and scanty objective findings abnormal T waves in each lead and widening and slurring of the QRS complexes indicate a serious myocardial involvement and a bad prognosis Often coronary stenosis can be diagnosed from the alterations of the electrocardiogram after exercise in patients who show a normal electrocardiogram at rest (Scherf)

Complications

Aortic Regurgitation One of the most common complications of simple aortitis is insufficiency of the aortic valves its symptomatology was discussed in connection with rheumatic aortic regurgitation Most of the findings are common to both lesions and the differentiation may be very difficult in some cases when a history of rheumatic fever or syphilitic infection is absent Furthermore the serologic reactions may be negative in syphilis and may be positive in patients with rheumatic aortic regurgitation The presence of narrowed orifices of the large arteries (differences in the pulsations of both carotid or both brachial arteries) is evidence of aortitis

It should be remembered that a rheumatic and syphilitic involvement of the aortic valves may coexist

Of great help is the old rule that the marked dilatation of the aorta in syphilitic aortic regurgitation permits the diastolic murmur in this lesion to be conducted better to the second right intercostal space while in rheumatic aortic regurgitation it is heard better at the lower left sternal border Although exceptions do occur the rule has clinical value

Aneurysms Aortic aneurysm another complication of aortitis will be discussed under a separate heading

Stenosis of the Coronary Ostia The third and most dreaded complication narrowing of the orifices of the coronary arteries is also of great importance It is a common event for it was found at postmortem examination in every third or fourth case of aortitis (Clawson) Often both orifices are involved sometimes one orifice is completely occluded and the other is just patent for a head of a pin or merely for a bristle Aortitis was presumably present in one of the oldest published cases of this type (Crooke) In a series of 1000 consecutive necropsies aortitis was present in 69 instances (Pincoffs and Love) In 15 of these 69 observations coronary stenosis was found Eight times both coronary arteries were involved in six instances only the right and in one case only the left was narrowed It is significant that 10 of these 15 patients died suddenly Woodruff found coronary stenosis in 27 per cent of aortitis discovered incidentally It was present in 57 per cent of those cases in which aortitis was diagnosed clinically because of symptoms In 39 per cent of these stenosis of both ostia was found

Stenosis of a coronary orifice or even its complete occlusion due to syphilitic aortitis is often tolerated without symptoms These changes are found accidentally at post mortem and were never suspected during life They must have existed for some time since the occlusion is created by old scar tissue The slow development of the coronary occlusion permits sufficient widening of a collateral circulation

The frequent occurrence of pain (decubital angina) in some cases may be considered as a sign indicative of coronary involvement In the majority of cases only pain on exertion i e typical effort angina exists and in these cases if aortitis is present one is permitted to assume a narrowing of the coronary ostia without further evidence Infarction of the heart muscle in cases of aortitis and coronary stenosis or occlusion is rare It is interesting that in these cases cardiac hypertrophy rarely develops (Cannon) presumably because of the diminished blood supply Furthermore dilatation of the heart and conduction disturbances in the electrocardiogram may be absent showing that the slow development of a syphilitic coronary obstruction allows ample time for the development of a collateral circulation and to provide sufficient blood supply to the specific tissue of the heart (Scherf and Boyd)

Syndromes have been described which may lead to the diagnosis of coronary stenosis in aortitis The rapid course of the lesion from the beginning of symptoms the lack of response to treatment the prominence and high incidence of anginal pain and the frequency of sudden death often permit the diagnosis of coronary stenosis In another group the diagnosis of marked stenosis of the coronary ostia confirmed at necropsy was made in four cases on the basis of the following syndrome (van Muijden and Scherf) An aortitis was present with or without aortic regurgitation The heart was normal in size or moderately enlarged The patients complained of pain behind the sternum and between the shoulders or

upper abdomen occurring on slightest exertion or excitement as well as frequently at rest and without apparent reason There was great anxiety and apprehension This anxiety may be the chief complaint in the absence of all other symptoms The anxiety was associated with an inexplicable restlessness All these complaints were immediately abolished by nitroglycerin In these cases the blood pressure rose only slightly during an attack of anginal pain in more advanced stages it fell sometimes to very low values This fall of blood pressure may precipitate a state of anxiety The slightest exertion leads to marked changes of the RS T segments and the T waves in the electrocardiogram

In patients with complete occlusion of only one coronary orifice and normal width in the other a normal electrocardiogram may be obtained even after exercise (Scherf)

Congenital Syphilis and Aortitis

Aortitis is rare in cases of congenital syphilis but many verified instances have been reported The affection of the aorta with the typical inflammatory changes in the media and adventitia was described long ago It seems that in most cases reparative processes take place if the child survives the first year and only exceptionally is there a progressive lesion with aneurysmal formation coronary stenosis or the development of an aortic regurgitation The lesion has been observed in a brother and sister with congenital syphilis (McDonald) In spite of the great tendency to spontaneous recovery the possibility of aortitis due to congenital syphilis must be considered in children and juveniles when the symptoms and signs discussed above are present

Course and Prognosis

The aorta seems to be infected within 12 months whenever treatment i insufficient (Coombs) Some evidence of an aortic lesion has been described as early as six to seven months after the infection (Carter and Baker While) but in a majority of cases years and even decades elapse before definite evidence of aortic disease appears In 10 per cent of a large series of cases the infection dated back less than five years (Cole and Usilton) An interval of 16 or even 20 years between infection and discovery of the first evidence of the disease is not rare but an aortitis might have existed for a long time before it was discovered

Of paramount importance is the fact that very benign cases exist and the disease may cease to progress at any stage It may remain asymptomatic or may run a very rapid course within a few weeks We have seen patients who claimed they felt normal until two or three weeks prior to the first examination yet who developed congestive heart failure did not respond to treatment and died a few weeks later Very often aortitis is an accidental finding at necropsy In patient who die from extracardiac causes a few suspicious spots may be seen in the aorta at necropsy on gross examination and only histologic examination confirms the diagnosis of syphilitic aortitis In many statistics compiled by pathologist these cases are included

The condition of the myocardium and of the orifices of the coronary arteries is of major importance for the prognosis If the orifices of the coronary arteries are narrowed sudden death frequently occurs Even if there is no history of anginal pain and the electrocardiogram is normal the tracings obtained after an exercise test may reveal a marked coronary stenosis

Because of modern therapy the statement that aortitis is ubiquitous insidious and disastrous is perhaps no longer correct The prognosis is said to be worse in colored patients and in those who are engaged in hard manual labor

Differential Diagnosis

In typical cases the diagnosis is easy For example a forty year old man or woman has a history of a syphilitic infection the serologic reactions are positive and the patient complains of anginal pain on effort Examination reveals a markedly widened aorta prominence of the ascending aorta to the right on x ray examination a tympanitic second aortic sound a rough systolic murmur over the aorta and scarcely palpable pulsations of the left carotid artery whereas the right pulsates strongly

However it has been stressed earlier that none of these signs is obligatory in aortitis Typical cases such as the one indicated above are exceptional The history and serologic tests may be negative and most of the signs mentioned may be absent Often the condition is oligosymptomatic and the positive diagnosis is difficult

In many patients under 50 (the younger the more surely) a dilatation of the ascending aorta calcification of the aortic knob a suspicious accentuation of the second aortic sound a systolic murmur over the aorta evidence of left ventricular hypertrophy and dilatation in the absence of hypertension lead to the correct diagnosis

Difficulties arise from the fact that hypertension is common in aortitis and practically all signs found can be attributed to the increased blood pressure alone This frequent combination of hypertension with aortitis makes it obligatory to consider aortitis in every hypertensive patient in whom no cause for the hypertension is found and in whose family there is no history of hypertensive disease However even if the possibility of an aortitis is considered it may be difficult or impossible to prove

Another problem arises in patients over 50 since we must differentiate between aortitis and atheroma If one realizes how difficult it often is even for the experienced pathologist to state on examination of the opened aorta whether a pure atheromatosis or a combination of atheromatosis and aortitis exists one will appreciate the problem the clinician faces In some cases the differentiation is possible only by histologic examination It is because of this frequent combination of aortitis with atheromatosis that the clinical and even the pathologic picture of aortitis described so many years ago found general recognition relatively late The widened aorta lime salt deposits in the aortic knob and the systolic

murmur in this area can be fully explained by the atheromatosis The same is also true of the elevated blood pressure in certain cases

Figure 90 shows calcium deposits in the ascending aorta and in the aortic knob in a 52 year old patient with syphilitic aortitis and an aortic regurgitation

All this leads to great diagnostic difficulties certainly in many cases the diagnosis is impossible But the number of correct diagnoses increases in many institutions whenever the rules discussed in the previous paragraphs are heeded On the other hand there are some investigators who assert that the diagnosis of uncomplicated aortitis is for practical purposes impossible (Kampmeier et al)

Midway between those who maintain that it is impossible to diagnose the lesion and those who risk making the diagnosis in patients with a simple atheromatosis there are authors who think the diagnosis is permissible only if (1) syphilis exists beyond any doubt (2) the aorta is definitely dilated (3) no other reason for aortic dilatation exists and (4) the patient is not over 40 years of age It is clear from the preceding discussion that the number of patients who fulfill these conditions is limited

If the results of recent investigations prove correct namely that efficient early treatment improves the prognosis prevents complications and prolongs life it is better to make an erroneous diagnosis of the lesion now and then than to overlook it completely because of too rigid criteria

Treatment

Prevention of aortitis in syphilitics seems possible with adequate treatment of the early stages In a large series of syphilitic patients it was found that a satisfactory treatment in the early stages was followed by aortitis in only 1 per cent of cases (Cole and Usilton) In another series (Vonderlehr and Usilton) no patient with cardiovascular syphilis was detected among those well treated and re examined 10 to 20 years after the infection The incidence of aortitis seems to increase in proportion to the inadequacy of the treatment in the earlier stages

Most cardiologists agree that patients with aortitis should receive antisyphilitic treatment If patients exhibiting evidence of aortitis are treated energetically *the progress of the lesion seems to be prevented or at least* the incidence of aortic regurgitation and aneurysm appears reduced However it is important to consider certain contraindications to treatment One of these is severe cardiac failure In such cases mercurial diuretics which also have an antisyphilitic action may be given In some of our patients an injection was administered weekly for three to five years for its diuretic action with much benefit and without untoward effects We would therefore suggest the consideration of this form of mild antiluetic treatment which also improves the circulation of the patient There are authors however who as soon as evidence of cardiac failure disappears use energetic therapy with penicillin

A very important contraindication is presented by the group of patients with angina pectoris It is assumed that the stenosis of the coronary orifice that exists in these cases will be increased by the treatment because the connective tis

sue will shrink Furthermore hyperemia of the inflamed tissue due to a Jarisch Herxheimer reaction at the beginning of the treatment may also increase the frequency and duration of the attacks Not rarely severe attacks of angina pectoris actually appear for the first time following therapy Observations have been reported however of disappearance of anginal pain during therapy

At present treatment with penicillin has superseded all the other previous therapeutic methods (salvarsan iodine bismuth) Procaine penicillin (1 200 000 units) is given daily until the patient has received six to nine million units Therapy is carried out in the hospital Herxheimer and paradoxical therapeutic reactions are observed regardless of the size of the initial doses No antecedent treatment with iodine is necessary Fever may be observed for a few days Slight decompensation is not considered a contraindication in several cases disappearance of slight anginal pain has been observed Only one series of treatment suffices Every patient with this disease who has not had penicillin before should receive this treatment once

There are no reliable statistics available as yet to prove that the dosage mentioned above suffices or that it stops progress of the illness

Heavy physical labor should be forbidden to patients with aortitis

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Chapter 24

Aneurysms

THE EXISTENCE OF ANEURYSMS has been known since the early description by Galen An aneurysm is a local widening of an artery with partial destruction of its wall there is proliferation of connective tissue from the adventitia and neighboring structures These features separate aneurysms from ectasia and dilatation of the arteries A distinction is also made between saccular aneurysms which are sharply demarcated from the normal part of the vessel and cylindric or fusiform aneurysms in which the separation is gradual although a large segment of the artery is usually involved

Arteriovenous aneurysms are not actual aneurysms and should be called arteriovenous fistulas Dissection of the aortic wall is still often incorrectly called an aneurysm

THORACIC ANEURYSMS

Etiology

The cause for aneurysms varies in different locations Most thoracic aneurysms are undoubtedly the result of syphilis but atherosclerosis bacterial infections (mycotic aneurysm) congenital malformations and trauma also play an etiologic role In recent years syphilitic aneurysms have become rarer while those caused by atherosclerosis are more common Formerly when the histologic changes in the thoracic aorta were studied the syphilitic variety was found in a majority of cases and nonsyphilitic thoracic aortic aneurysms were rather exceptional The incidence of syphilitic aneurysms has diminished in recent years

Aneurysms have been reported in patients with congenital syphilis In acquired syphilis the average time elapsing between the infection and discovery of the aneurysm is about 20 years but cases have been reported in which aneurysms were noted two years (Sanford) after the infection It was pointed out in the chapter on aortitis that syphilitic invasion of the aorta always begins within the first two years after infection

Incidence

In a study of 5000 cases reported in the literature thoracic aneurysm was found to be the cause of death in 0 13 per cent of individuals in large American cities This figure must be amended however since many statistics were compiled by coroners who investigated death under unusual circumstances (Boyd) Irr

spective of its former incidence there is no doubt that energetic treatment of the early stages of syphilis has made the condition much rarer at present

Aneurysm of the thoracic aorta occurs about five times more often in males than in females In Negroes the incidence is about five times higher than in the white population

Aneurysms occur at all ages Examples have been reported in children as well as in men over 90 years of age (Willson and Marcy) The maximum incidence however is between 36 and 40 years in males while in women the peak occurs in a group about 10 years older (Boyd) In Negro patients aneurysms appear in younger age groups

Pathology

Usually aneurysms are single but multiple aneurysms are not rare In one series two to five aneurysms were found in 20 per cent of the affected patients (Lucke and Rea) In another series however multiple thoracic aneurysms were seen only 23 times in 633 cases (Kampmeier)

Syphilitic aortitis mainly involves the media Destruction of the muscle cells and elastic fibers weakens the wall so that intra aortic pressure causes bulging The original wall may be completely destroyed and reactive inflammation in the adventitia plus pressure on neighboring tissues causes new layers of fibrotic tissue to form Thrombi develop within the aneurysmal sac and may fill it completely Secondary deposits of calcium in the thrombotic mass and in the remaining parts of the aorta are common

If the thoracic aorta is divided into the ascending aorta the arc the border between the arc and the descending aorta and the descending aorta proper the incidence of aneurysms is 10 to 7 to 3 to 1 respectively Another aid to the understanding of the development of aneurysms in the thoracic aorta is furnished by the so called surge line which connects the sites at which the impact of the blood on the aortic wall is strongest Directly above the valves this area is situated on the anterior wall of the aorta As the aorta ascends this line moves laterally to the right in the arc it is approximately in the center of the vessel passing from here to the left posterior aspect of the wall where the descending portion of the aorta begins In the lower part of the descending aorta it lies in the middle of the posterior wall Although exceptions are not rare this line connects the favorite locations of thoracic aneurysms

Aneurysms of the Sinus of Valsalva Aneurysms of the intrapericardial portion of the aorta may originate from the sinus of Valsalva Often they are very small These aneurysms may be situated in any of the sinuses but involve the right sinus most frequently they are usually the result of a congenital anomaly Occasionally these aneurysms are of syphilitic origin the result of atherosclerosis or a complication of subacute bacterial endocarditis particularly with bicuspid aortic valves They are more common in men

Aneurysms of the right sinus develop anteriorly and may cause erosions of the sternum and ribs They may cause a shadow to the right of the aorta and

occasionally are distinguished from aneurysms of the ascending portion of the aorta radiologically by the very small base which connects the shadow with the aorta Occasionally these aneurysms are so small that roentgen findings may be normal They develop often within the cardiac shadow These aneurysms may rupture into the right atrium or ventricle Aneurysms of the left sinus of Valsalva may be visible on the left side at the area of the pulmonic artery and may penetrate the left ventricle Rupture into the pericardial cavity and into the venae cavae also occurs The latter event causes the sudden appearance of cardiac murmurs over the base cyanosis and edema An aneurysm of the anterior sinus can cause pulmonary stenosis or tricuspid stenosis because of compression An aneurysm of the right lateral sinus can bulge into the right or left atrium

The murmurs in this lesion are continuous like those of patent ductus arteriosus Before perforation takes place the diagnosis is difficult

Symptoms

Aneurysms of the thoracic aorta were divided into aneurysms of symptoms and aneurysms of signs because according to location symptoms appear very early in one group while only objective signs without symptoms tend to occur in the other The former type occurs more often in the ascending aorta the latter in aneurysms of the transverse portion

The most common symptom is pain Often it is an angina on effort because stenosis of the coronary orifices is present Erosion of the ribs sternum and vertebra causes rest pain which may be excruciating particularly at night the site of this pain necessarily varies with the structures involved When pressure is exerted on nerve trunks intractable neuralgia appears Sometimes pain is referred and when noted in the left shoulder it is mistaken for an arthritis bursitis and the like

Second in frequency among the symptoms is dyspnea caused by pressure on the trachea or large bronchi It is usually of the inspiratory type similar to dyspnea caused by an obstruction of the upper air passages

If myocardial disease causes left ventricular failure paroxysmal nocturnal dyspnea occurs

Cough is common and represents the first and chief complaint in about 20 per cent of cases In many instances the history relates a series of colds the last one of which persisted Sometimes — with paralysis of the recurrent laryngeal nerve — the cough is brassy Often it is non productive Pressure of the aneurysm upon a large bronchus may however result in bronchostenosis and may cause distal bronchiectasis so that a profuse bronchorrhea and productive cough develop Secondary infections may alter the character of the sputum

Dysphonia (hoarseness) and dysphagia aid in locating the site of an aneurysm (transverse portion of the aorta) Dysphagia is not common since the esophagus is very mobile and easily escapes pressure in order for this symptom to appear, the aneurysm must bulge posteriorly just beneath the bifurcation of the

trachea Dysphagia usually does not occur in aneurysms of the lower descending thoracic aorta even if the aneurysm ultimately ruptures into the esophagus

Hemoptysis may occur early in the form of blood streaked sputum It may precede rupture of an aneurysm into a bronchus by several months

Palpitation is an infrequent symptom and too vague to aid in the diagnosis of aneurysm

In a relatively small number of cases the patient notices a mass bulging through the anterior chest wall Profuse perspiration due to pressure upon the sympathetic nerves herpes zoster and hiccough are sometimes early and non characteristic complaints If blood is aspirated into the lung and secondary infection develops fever and signs of bronchopneumonia may appear

Signs

Inspection may reveal edema of the face neck and upper extremities with appropriately located aneurysms Sometimes congestion of the veins in the same areas and a marked diffuse cyanosis also exist These signs are caused by compression of the superior vena cava Cyanosis is particularly marked when an aneurysm ruptures into the superior vena cava Compression of a single vein such as the right or left innominate vein may cause cyanosis limited to a circumscribed area

Sometimes a large tumor bulges on the upper right parasternal area through the sternum or to the left of it Classical expansile pulsations are not always present in this mass Secondary reactive inflammation of the tissue may cause a local increase of temperature in this area if as often happens the overlying skin is red and the aneurysm points like a boil the aneurysmal mass may be mistaken for an abscess an error by no means uncommon in the preroentgenologic era

Tracheal tug may be found in connection with aneurysms of the transverse portion of the aorta but it is by no means pathognomonic The neck veins may be markedly engorged A thrill or abnormal pulsation may be detected over the site of the aneurysm and abnormal dullness is also a common finding in this location A systolic murmur may be heard particularly in aneurysms of the ascending aorta this murmur is heard far to the right of the sternum Diastolic murmurs are also found without intrinsic involvement of the aortic valve owing to aortic regurgitation from distortion of the valvular ring Asymmetry in the pulsations of the carotid and brachial arteries and delayed pulses are often advanced as evidence of aneurysm It was pointed out however in the preceding chapter that aortitis without aneurysmal dilatation also produces this sign It is common in aneurysms since aortitis is always present when syphilis is provocative

Examination of the heart may yield normal findings despite a huge aneurysm This holds particularly for aneurysms at some distance above the supra valvular portion of the aorta for the aortic valves and coronary ostia are usually normal in these cases Pressure upon the azygos vein may cause marked right pleural effusion

Unilateral exophthalmus and mydriasis or enophthalmus with miosis (Horner s syndrome) appear with irritation or paralysis of the sympathetic nerves

Aneurysms may cause a paralysis of the right phrenic nerve with elevation and immobility of the right half of the diaphragm

Some of the symptoms and signs enumerated will lead to an x ray examination which usually provides positive evidence of an aneurysm It must be stressed however that the differential diagnosis from other mediastinal tumors may be difficult particularly when the clinician must rely upon physical signs alone Pulsations may be found in nonaneurysmal structures while a true aneurysm containing a large thrombus in its sac need not pulsate A small aneurysm that develops dorsad is especially likely to escape detection

In many cases the diagnosis of an aneurysm can be made only by an expert radiologist after prolonged observation Usually fluoroscopy is more satisfactory than roentgenograms The finding of calcium deposits in the tumor mass often facilitates the x ray diagnosis No fluoroscopy is complete without examination of the esophagus filled with a suspension of barium The trachea is often displaced *to the left and a main bronchus may be visibly compressed* Secondary pulmonic changes are discovered on x ray examination Careful study of the thoracic cage may reveal early evidence of bony erosion particularly of the vertebra in aneurysms of the descending aorta

The electrocardiogram is normal or — with stenosis or occlusion of the coronary ostia — altered as in other forms of coronary disease

Differential Diagnosis

While easy or obvious in some cases the diagnosis of the lesion presents *great difficulties in others The clinical picture is extremely variegated* Confusion with other conditions was frequent before the roentgenologic era and occurs even today

Rheumatism arthritis asthma and chronic bronchitis are the most common diagnostic errors in these cases The lesion is also confused with bronchogenic carcinoma from which it can sometimes be differentiated only with great difficulty Angiocardiography may be necessary A carcinoma of the esophagus may be wrongly diagnosed if the aneurysm is too small to be seen but causes esophageal symptoms It occasionally happens that patients are treated for a simple laryngitis if they complain only of hoarseness

Course of the Disease and Mode of Death

Aneurysms are a severe affliction and the prognosis is poor Patients with huge aneurysms may lead an active life for years but such cases are exceptional Statistics on the duration of the disease are limited only to the estimated duration after the appearance of symptoms usually the lesion has existed for a much longer time In the majority of cases death occurs within two years after the onset of symptoms but patients are known whose aneurysms were observed for *20 or 30 years (Boyd) Instances of healing of the aneurysm by spontaneous* obliteration of the sac through organization of the thrombus are so rare that they are listed among the curiosities of medicine

About half of the aneurysms of the thoracic aorta terminate by rupture Most of the remaining cases die from the mechanical effects of pressure on various organs Only a small percentage of patients die from unrelated disease

External rupture of the aneurysm is uncommon even when there is a large protruding mass In a series of 1197 cases of rupture of a thoracic aneurysm external rupture occurred only 61 times (Boyd) In aneurysms of the ascending aorta intrapericardial rupture occurred in one third next in frequency was rupture into the left pleura the left bronchus and into the esophagus Rupture may also occur into the right pleura right main bronchus the pulmonary artery or the superior vena cava (causing a sudden and marked increase of cyanosis) Aneurysms of the arc often rupture into the trachea a bronchus or the esophagus Aneurysms of the descending aorta usually rupture into the left pleural cavity left bronchus or esophagus For a more detailed description of all possibilities reference should be made to reviews of the literature on this subjects

Rupture into the pulmonary artery causes sudden collapse shock progressive dyspnea a constant murmur and thrill in systole and diastole in the second or third left intercostal space parasternally pulsus celer and right ventricular failure

Rupture into the superior vena cava causes a similar thrill and murmur to the right of the sternum and signs of superior vena cava obstruction

Rupture through a serous surface (pleura pericardium) occurs without warning and causes sudden death Rupture through a mucous membrane (esophagus trachea) may give warning in the form of slow bleeding or oozing Sometimes bleeding even if rather profuse is not immediately fatal but a lethal hemorrhage may occur a few days afterward

ANEURYSMS IN OTHER LOCATIONS

Aneurysm of the Innominate Artery

These aneurysms develop near the right sternoclavicular articulation Pain and throbbing in the neck constitute the chief symptoms The aneurysmal sac is usually palpable and a thrill is found The right jugular vein may be distended and edema of the right side of the face may appear The right carotid and right brachial pulse are smaller

It has been pointed out that elongation of the aorta with high position of the innominate and right subclavian artery and kinking of the carotid artery are often confused with these aneurysms

Aneurysm of the Pulmonary Artery

This is a rare lesion In two thirds of the observed cases the common trunk of the pulmonary artery was affected (Boyd and McGavack) In nearly one half of the cases reported one or more congenital abnormalities such as patent ductus arteriosus stenosis of the pulmonary orifice and atrial septal defects were present Syphilis is an etiologic factor in the acquired variety

arteriosclerotic mycotic and traumatic aneurysms though well known are less common

There are no characteristic symptoms Palpitation is present early while cyanosis and dyspnea appear later The diagnosis can be made if a pulsation and a systolic thrill are found on the left side parasternally in the area of the second or third intercostal spaces with a loud systolic murmur, and if x ray examination shows a marked and circumscribed dilatation of the pulmonary artery

Even with x ray examination differentiation from an aneurysm of the aorta is sometimes impossible since aneurysms of the ascending aorta may develop on the right side and simulate dilatation of the pulmonary artery The presence of hilar pulsation may help in the differentiation

Undoubtedly many patients in whom the diagnosis of aneurysm of the pulmonary artery has been made without postmortem confirmation in reality had an atrial septal defect

Aneurysms of the Abdominal Aorta

These aneurysms are about as common as those of the descending portion of the thoracic aorta They appear however in an older age group that is in patients over 50 Arteriosclerosis is the most common cause Syphilis is not rarely responsible for these aneurysms whereas other infections such as tuberculosis are exceptional etiologic factors In one series (Mills and Horton) evidence of syphilis was found in 8 8 per cent while the incidence of syphilis in another series was placed as high as 58 per cent (Scott) In abdominal aneurysms lesions are multiple in 18 to 20 per cent of the cases Trauma is rarely responsible

The aneurysmal sac is often located in the anterior aortic wall just below the diaphragm particularly in aneurysms of syphilitic origin Arteriosclerotic aneurysms lie at the celiac axis for the most part

The chief symptom is abdominal pain which may be overwhelming and which may appear in paroxysms lasting minutes or hours The pain is throbbing and appears particularly at night or after a meal The pain may spread to the thigh the scrotum or the labia as in a kidney stone In addition to the pain nausea and vomiting often occur Obstipation and meteorism are common Reactive inflammation of the surrounding tissue may cause peritoneal irritation The aneurysm may compress the stomach a part of the intestines or a ureter causing corresponding symptoms Erosion of the vertebrae and compression of the spinal cord may produce hemiparesis or paraplegia

A pulsating tumor the size of an orange or even larger is often found on palpation It must be emphasized that the mere fact a tumor pulsates does not by itself confirm the diagnosis The pulsating mass must be wider than the normal aorta Evidence of expansile pulsation in all directions is necessary because the pulsation may be transmitted The tumor is often tender on palpation Occasionally a murmur is heard and a thrill is felt over the aneurysm

Flat x ray plates of the abdomen are a great diagnostic help The aneurysm is often outlined by the deposits of calcium present in the aneurysmal wall Erosion of the vertebrae is occasionally noted in lateral plates With tomography one may find a soft tissue mass

The duration of the lesion depends upon its size and location Usually rupture takes place in six to twelve months after the appearance of symptoms but cases of much longer duration are known In one group of statistics 20 per cent of abdominal aneurysms without complaints survived for five years

At times the rupture occurs into the duodenum or the abdominal cavity Not rarely the rupture is retroperitoneal Patients may survive this type of rupture for a few days often in a deepening coma In not a few patients the course of the disease is interrupted by episodes simulating peritonism or ileus which subside after several days

One must make sure not to confuse an abdominal aneurysm with a strongly pulsating normal abdominal aorta which is easily felt in patients with enteroptosis

Aneurysms of Peripheral Arteries

The majority of these aneurysms are of embolic mycotic origin The etiology is usually a bacteremia in the course of subacute bacterial endocarditis chronic empyema or osteomyelitis The infected emboli lodge in the vasa vasorum Small mycotic aneurysms that occur in the aorta are usually not diagnosed clinically they are more often found in the peripheral arteries Rupture is a common event before these aneurysms reach large dimensions Nearly one third of these patients are under 20 years of age The lesion is often overlooked if it occurs in a peripheral artery it is often confused with phlebitis

Erosion of an artery by an extrinsic process leads to the formation of an aneurysm in rare cases

Syphilitic aneurysms also occur at times in peripheral arteries Thus aneurysm of the popliteal artery was rather common and was perhaps next in frequency to aneurysm of the aorta We observed a syphilitic aneurysm in the radial artery

Congenital aneurysms especially common in the cerebral arteries stem from malformations of the arterial wall They are most often situated at the circle of Willis They may cause sudden hemiplegia with xanthochromic spinal fluid and severe occipital headache These accidents need not occur until adult life is reached Some patients are over 40 years of age when symptoms appear The dramatic picture of a subarachnoid hemorrhage may also be the result of a rupture of a congenital cerebral aneurysm

Similar congenital miliary aneurysms have been observed in the coronary arteries otherwise an uncommon site of aneurysm coronary artery aneurysm may be due to periarteritis nodosa In unusual instances it follows stab wounds Congenital aneurysms of the coronary arteries are often multiple sometimes rupturing or becoming thrombosed

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DISSECTION OF THE AORTA AND CYSTIC MEDIONECROSIS

Separation of the coats of the aorta or dissecting aneurysm was observed by Morgagni and was well known to Laennec In the past the diagnosis was made only at postmortem examination The number of cases in which correct clinical diagnosis is made has increased since Shennan s excellent monograph was published The term dissection of the aorta is preferable to dissecting aneurysm

Incidence

It has been estimated that the lesion occurs once in about 400 necropsies (Sailer) or once in 480 autopsies of patients over 20 (Gouley and Anderson) In another series of 3129 autopsies 12 dissecting aneurysms were found There fore the condition is not extremely rare While it has been seen in an infant of 14 months and in a 100 year old woman it is most common in males after the age of 60 It is more common in hypertensive patients than in those with normal pressure although this has been denied by some

In young women dissection of the aorta has been observed particularly during pregnancy and in the presence of coarctation of the aorta It was observed in a 34 year old woman and her 14 year old son Eighty per cent of the patients are beyond 60 years of age and 65 per cent are males

Pathology

Hemorrhage between the layers of the aorta may occasionally follow trauma erosion of the aorta by an abscess tumor or arteriosclerotic changes (atherom atous ulcer) but the most common cause is medionecrosis cystica of the aorta (Erdheim Gsell)

This lesion is recognized as the outstanding cause of spontaneous rupture of the aorta and of the dissecting aneurysm It is usually limited to the ascending aorta Small areas of degeneration develop in the inner part of the media without any sign of inflammation According to some investigators the change involves primarily the elastic fibers and the connective tissue according to others the muscle fibers are affected first Later an over production of mucoid material and the formation of cysts may be seen These focal mucoid changes and necroses in the aorta were described before but their relation to the dissecting aneurysm remained unknown until the publication of more recent pathologic investigations (Erdheim) The absence of evidence of inflammation distinguishes the lesion from aortitis while the localization in the media with the intima remaining intact separates it from atherosclerosis On gross examination the lesion often resembles syphilitic aortitis

The etiology of the process is unknown It possesses some similarity to experimental necrosis of the media of the aorta seen in rabbits following injections of epinephrine Therefore excessive strain and stress have been alleged as causative Others think that infectious di eases such as scarlet fever or typhoid fever are responsible Marked damage of the arteries in infectious diseases has

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Evidence ... of blood supply in the lower extremities may be ... if the ... and their branches are affected. A bruit and thrill may appear ... arteries (Logue). The local picture may resemble that of a peripheral ... or thrombosis. In addition to the clinical findings already ... in the pleural cavity, vomiting, nausea and ... rhythm.

Examination ... heart often reveals a systolic and a diastolic murmur. The latter ... feature in patients with a typical evolution of the syndrome ... displacement of the aortic valves when the dissection involves the ... an event which occurs in more than 70 per cent of the ...

Rupture ... mediastinum causes aphonia and dysphagia. Hemoptysis is common ... unexplained.

Roentgen ... examinations have been made repeatedly but naturally only in the ... patients who survive for a while. Widening of the aortic knob and its contour in the ... and abnormal shadows along the large vessels of the cardiac base may be seen. Sometimes these shadows pulsate. X-ray examination helps to establish the diagnosis.

Differential Diagnosis

The picture of the condition is protean and presents great diagnostic difficulties; the number of cases in which the diagnosis is reached ante mortem is increasing but still is not large.

The excruciating pain presented by patients is usually confused with the pain of coronary occlusion and myocardial infarction. It is pointed out by various authors that the pain in dissecting aneurysms is more knifelike than compressive or vise-like; the wandering of the pain down the back may help in the differentiation, but this symptom is often missing or late in appearance.

The elevated temperature, leukocytosis, pericardial involvement, electrocardiographic changes and fall of blood pressure are found in both conditions. The blood pressure, however, usually remains high in dissecting aneurysm. This fact, together with the appearance of a diastolic aortic murmur and the absence of pulsation in one carotid or brachial artery, will help in the diagnosis. The absence of electrocardiographic changes in coronary occlusion is rare; the presence of changes that indicate a myocardial infarction in dissecting aneurysm is unusual. The differentiation may be easier if the patient survives for several hours, but often is impossible at the onset of symptoms. Since the immediate treatment consists of an injection of morphine in both conditions, nothing is lost from a therapeutic standpoint. The differentiation is, however, important for prognosis.

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been described (Wiesel) The frequent occurrence of vascular lesions in rheumatic fever has been pointed out before but these lesions are of a different type Both the excessive use of tobacco and the occasional presence of syphilis were considered etiologic factors Toxins of unknown character are also supposed to be causal

Medionecrosis is common It has been seen in 95 cases among 210 routine necropsies (Rottino) The incidence is higher with increasing age and with increasing blood pressure

The vasa vasorum in the aorta suffer in this process It seems probable that rupture of the vasa vasorum leads to a hemorrhage between the layers of the media If this hemorrhage extends it may lead to complete rupture of the weakened aortic wall More often the tears run up and down the aorta causing the dissection The intimal wear is thus a point of emergence and not as it was believed for many years a point of entrance and the beginning of the dissection (Sailer) In favor of this conception is the fact that dissecting aneurysms have been seen in which the intima was intact Core and Seiwert report 23 instances in which there was no intimal break The tear has two points of predilection explained easily by the anatomic situation One is just above the aortic valves that is 2 to 4 cm above the sinus of Valsalva the other is in the area of the aortic isthmus In coarctation of the aorta dissection is not rare The tear in the ascending aorta is usually transverse

The separation of tissue of the media (which takes place chiefly in the outer layers) may proceed centrally toward the heart and occlude the coronary arteries Usually the dissection burrows peripherally and all arterial branches originating from the aorta can be involved At first they remain connected with the main stem of the aorta by the thin intima alone but soon the vessel is occluded and severed at its origin This may happen to the innominate artery the left carotid artery and left subclavian artery to the intercostal and lumbar arteries the renal and mesenteric arteries and so forth The dissection may proceed down to the femoral and even to the popliteal vessels In a 15 year old boy the dissection reached the posterior tibial artery in one side and the popliteal artery on the other There was also some dissection of the pulmonary artery (Gardner et al) Since the dissection rarely involves the whole circumference of the wall of the aorta not all aortic vessels are involved during the progress of the lesion

The dissection may re enter the lumen of the aorta at any point or rupture into the surrounding area If the blood re enters the aorta the patient occasionally survives and an endothelial lining forms in the new path These patients have a double barrelled aorta If the entire circumference of the aorta is involved in the whole path of the aneurysm the inner part of the aorta may be carried down toward the periphery as an embolus If the dissection breaks outward — a common event — severe hemorrhage may occur into the pericardium the mediastinum the pleura or abdomen resulting in sudden death

Incomplete rupture of the aorta (as well as complete rupture) has a similar underlying pathology Incomplete rupture may also cause the sudden appearance

of an aortic diastolic murmur (Peery) Of great interest is the production of the lesion in rats fed lathyrus odoratus (sweet pea seeds) (Bachhuber and Lalich) or aminonitriles (Wawzonek et al) The toxic substance is beta aminopropionitrile (Bean and Ponsetti) Kyphoscoliosis and hernias may coexist showing a tendency to a connective tissue injury

Symptoms and Signs

The most outstanding symptom is the sudden and overwhelming pain which strikes the patient with full force and without premonitory symptoms often beginning during physical work Some believe that a sudden rise of blood pressure may be an initiating factor responsible for dissection The pain is knifelike and often spreads to the shoulder or is felt only between the scapula Sometimes it wanders down with the progress of the dissection Occasionally it extends into the right or left arm At times it is intermittent sometimes it is mild or even completely absent Baer et al missed the pain in 20 out of 44 cases Usually there is no compressive sensation as exists in anginal pain due to myocardial infarction If the pain is felt only in the back or in the abdomen confusion with other lesions may arise In general the location of the pain depends upon the site of the aortic lesion

Vomiting and nausea as well as profound shock occur often the clammy skin is covered with sweat Dizziness appears and the patient may lose consciousness this happens particularly when one carotid artery is involved and suddenly becomes occluded Convulsions occur as well as disorientation and dyspnea

The blood pressure may fall the temperature rise and there is a marked leukocytosis which may reach 30 000 white cells with more than 90 per cent polymorphonuclear cells

Most of the other symptoms and signs naturally depend to a great extent on the location and spread of the dissection and the vessels involved

Dissection toward the heart may cause occlusion of coronary arteries with myocardial infarction and all its consequences The electrocardiogram then shows the changes expected in a myocardial infarction and a pericardial friction rub may appear Rupture of the dissection is particularly common and may cause the clinical syndrome of cardiac tamponade it soon proves fatal

The innominate artery may escape but the left subclavian and left carotid artery are often compressed or occluded This may lead to hemiplegia hemiparesis or paralysis of one limb and other neurologic phenomena The left arm may become pale and bloodless and the pulsation of its arteries disappears

Dissection of the intercostal and lumbar arteries may lead not only to pain that gradually wanders down the back but also to such segmental neurologic findings as hyperesthesia or anesthesia Paraplegia is also observed The dissection of the intercostal arteries and occlusion of branches supplying the anterior aspect of the spinal cord may account for the overwhelming weakness of the legs a common and major complaint

Involvement of the renal arteries leads to renal infarction renal hemorrhage anuria and uremia Bloody stools may appear and the picture of an acute abdomen

is presented when the mesenteric arteries are involved or the dissecting aneurysm ruptures into the abdomen

Evidence of a disturbed blood supply in the lower extremities may be found if the femoral arteries and their branches are affected A bruit and thrill may appear over the femoral artery (Logue) The local picture may resemble that of a peripheral arterial embolism or thrombosis In addition to the clinical findings already mentioned are blood in the pleural cavity vomiting nausea and gallop rhythm

Examination of the heart often reveals a systolic and a diastolic murmur The latter a characteristic feature in patients with a typical evolution of the syndrome results from displacement of the aortic valves when the dissection involves the ascending aorta an event which occurs in more than 70 per cent of the cases

Rupture into the mediastinum causes aphonia and dysphagia Hemoptysis is common and not well explained

Roentgenologic examinations have been made repeatedly but naturally only in those patients who survive for a while Widening of the aortic knob a double contour in this area and abnormal shadows along the large vessels of the cardiac base may be seen Sometimes these shadows pulsate X ray examination rarely helps to establish the diagnosis

Differential Diagnosis

The picture of the condition is protean and presents great diagnostic difficulties the number of cases in which the diagnosis is reached ante mortem is increasing but still is not large

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time the presence of a Corrigan pul e an increased pul e pressure and a dia tolic aortic murmur in the second right intercostal space parasternally may cause confusion with syphilitic aortic regurgitation

For obvious reasons the disorder may be mistaken for a cerebral accident a pleural effusion renal di ease an abdominal lesion and particularly a surgical emergency

The differentiation is especially difficult if there is no pain or if the pain is not felt within the chest If patients complain only of weakness in the legs or abdominal colic with diarrhea or pain in the back the diagno is will be possible only for those who are thoroughly familiar with the picture and think of it The *disappearance of peripheral pulses the wandering of the pain down along the aorta* and the appearance of a diastolic aortic murmur are the best diagnostic signs

Prognosis

The prognosis is very bad Only 7 per cent of Shennan s patients lived for 1 to 5 weeks Healed cases usually with a double barelled aorta are rare but survival for several years is observed (Hoskin and Gardner) In some of these patients no history could be elicited pointing to the date of dissection Apparently it proceeded without pain and did not make the patient sufficiently ill to require rest in bed In most patients even when they survive for a time the dissection resumes its course and causes perforation and death

Treatment

As pointed out before morphine is indicated to relieve the pain Complete rest is advised and enforced with the administration of barbiturates and other sedatives Oxygen has been repeatedly recommended but its value is dubious An operation designed to relieve pressure from a compressed femoral artery was attempted (Gurin et al) and an attempt was made apparently successful to operate on some patients in the hope of diverting the blood and causing its re entry into the aorta (de Bakey et al) It is in this way that self healing occurs in aortic dissection — spontaneous re entry

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Chapter 25

Atheroma of the Aorta and Atherosclerosis of Smaller Arteries

ARTERIOSCLEROSIS APPEARS in three main forms as atherosclerosis in the aorta and many large arteries as the harmless media sclerosis and as arteriolosclerosis of the small arterioles in hypertension

Atheroma of the Aorta This lesion begins early in childhood it becomes well developed in the fifth decade and varies only in degree in different individuals It is not however a physiologic phenomenon As in other forms of atherosclerosis the etiology is unknown although a disturbance of lipid metabolism is frequently assumed In this purely degenerative process lipid infiltration degeneration with necrosis and intimal proliferation are combined secondary calcification takes place The aorta or any involved artery becomes elongated and tortuous If an atheromatous placque ruptures debris is sent toward the periphery and causes embolism Sometimes an aneurysm forms an event observed particularly in the abdominal aorta

Pure atheroma causes no symptoms and the condition may progress very gradually without any important disturbance of the circulation Often it is an incidental finding

With advancing age the elasticity of the aorta diminishes The normal aorta has a storage function It receives the output from the left ventricle and moves it slowly toward the periphery with the aid of its elastic and smooth muscle fibers In this way the blood flow which receives rhythmic impulses by the contraction of the left ventricle becomes steadier The ascending aorta acts as a compression chamber With increasing age diminished elasticity of the aorta and atherosclerosis this function of the ascending aorta disappears and with it the systolic blood pressure rises while the diastolic tends to fall The size and shape of the heart remains normal A systolic murmur is audible over the aorta and is often transmitted to the apex as are all systolic aortic murmurs In elderly patients with emphysema the basal murmur at the second right interspace disappears while the systolic murmur over the apex remains and may cause confusion with other murmurs Often the systolic apical murmur is created by a sclerosis of the mitral valves while the systolic aortic and apical murmurs may be caused by atherosclerosis of the aortic valves The systolic aortic murmur is often midsystolic that is sharply separated from the first sound by an interval It may appear at the end of systole (figure 91) The second aortic sound is accentuated and may even be metallic or ringing as in aortitis

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Atherosclerosis of the larger renal arteries may cause contraction (athero sclerotic contracted kidney) and scars but it rarely disturbs renal function It is asymptomatic Albuminuria is a common sign

Aneurysms due to atherosclerosis have been discussed in the preceding chapter

Therapy No treatment is known A well regulated life may add to the patient s comfort and lessen the opportunity for various vascular accidents The individual should adapt himself to a slow pace — avoidance of excesses of food and drink elimination of sudden strains either physical or mental and so on The amount of fat in the food should be small Eggs cream butter and margerine are forbidden

The time honored prescription of iodides is still widely used in some countries As a rule such drugs are harmless and often beneficial especially in cerebral vascular sclerosis Since arterial changes following the feeding of cholesterol to rabbits can be prevented by the administration of iodides the empirical use of this drug may have some rationale

Chapter 26

The Cardiovascular Neuroses and Neurocirculatory Asthenia

IT IS DOUBTFUL whether a sharp line of demarcation can be drawn between cardiovascular neurosis and neurocirculatory asthenia We prefer to discuss the two conditions as separate entities even though there are many strong arguments against the appropriateness of such a division

CARDIAC NEUROSIS

The cardiac neuroses are among the problems rarely encountered in the hospital but often met in private practice An extremely variegated picture is involved Recognition of the condition is often difficult and treatment requires much experience tact and knowledge of human nature Undoubtedly many cases were formerly included which did not belong in this group In old treatises on this subject extrasystoles paroxysmal tachycardias and even angina pectoris were diagnosed and discussed as cardiac neuroses Until recently several disturbances found in women and connected with ovarian dysfunction that are now *quickly and successfully treated with estrogens were attributed to* a neurosis

The complaints are diverse Palpitation dyspnea and precordial pain stand in the foreground as they do in many organic heart diseases The experienced physician however will discover by a few questions that the palpitation and pain are independent of effort they appear on excitement or without any external reason and they may last for hours The respiration may be completely irregular if dyspnea is present it may be purely subjective and without discernible change of rate or depth of the respiration Insomnia inability to concentrate or work a tendency to perspire readily anxiety and restlessness supplement the picture Outwardly these patients may seem very quiet many of them do not present the picture designated by laymen nervousness The pain rarely radiates to the arm and it is equally unusual for it to be retrosternal More often it is inframammary or near the apex

The signs and differential diagnosis will be discussed in connection with neurocirculatory asthenia since in this condition similar complaints are offered and the same signs are found

Patients with cardiac neuroses with any neurosis for that matter are *patients* and must be treated as such They suffer from their distress and their families suffer *with them For this reason it is entirely wrong* to tell the patient that his complaints are only imaginary An unpleasant situation is created

when the patient is told there is nothing wrong with him that all complaints are purely nervous and the family is informed by the physician that the patient is hysterical It is much better to explain to the patient and to his relatives in keeping with the facts that no *organic* heart disease is present the disturbance is not dangerous nor will it lead to complications rather an alteration of the cardiac nerves and of the nervous regulation of the heart is present which merits careful consideration and requires careful treatment however *it is definitely curable and will have no consequences* Many neuroses vanish as soon as the relatives adopt a different attitude toward the patient upon the advice of the physician

In treating this type of patient it is not advisable to rely chiefly on medicinal therapy Bromides chloral hydrate preparations of valerian and the modern tranquilizers are excellent supportive agents but they have little value by themselves Psychotherapy is much more important For this purpose much experience is necessary but special training is not indispensible Careful interrogation and detailed inquiry into the symptoms should establish a close contact between physician and patient Often one will succeed in discovering domestic strife professional dissension or material or sexual preoccupations as the source of initiating factors in the neurosis Corresponding counsel explanation and encouragement will aid remarkably Hardly ever does one have the satisfaction of having helped so much and hardly ever does one acquire so thankful a patient *as in this oft neglected group*

Neurocirculatory Asthenia

This condition is also known as Da Costa s syndrome irritable heart soldier s heart and autonomic imbalance As indicated earlier we are dealing here with a syndrome that cannot be distinguished from a cardiac neurosis

Occurrence Frequency

While the disorder is occasionally encountered in times of peace it seems to be particularly prevalent during wartime and when people are under stress and strain Da Costa originally described the condition during the Civil War About 44 000 cases became pensioners because of this disease in Great Britain during the First World War (Parkinson) Out of every 10 patients admitted to a hospital allocated for the care of cardiac patients in the period 1914—1918 nine suffered from neurocirculatory asthenia or D A H (disordered action of the heart as it was called by the British Army) (Lewis) There is evidence to show that more than 1 5 per cent of the rejections by draft boards in the United States during the recent war were due to neurocirculatory asthenia In the Second World War one out of every ten soldiers admitted to hospitals for cardiac complaints had neurocirculatory asthenia

Naturally men are more often affected in time of war when the ratio seems to be 3 to 2 in favor of males This figure may be reversed in times of peace About 30 per cent of the patients are engaged in hard labor (Hill and Dewar)

Symptoms

Fatigue A regular and outstanding symptom is great fatigue Characteristically the patients complain of it when awakening in the morning after a long sound sleep This profound exhaustion makes the patient dread any activity In mild cases as in all neurotics the feeling of fatigue may vanish during the day If the patient is active he tires easily

Dyspnea This is a common complaint It is described as the sensation as if the breath would not go through and has been discussed in the first chapter The hyperventilation syndrome is common

Pain Sometimes stabbing pain is felt in the inframammary region or more rarely behind the sternum It may radiate to the left arm and thus may be very misleading Like the pain in other cardiac neuroses it bears no relation to effort it does not come during the excitement but hours afterward The area over the left breast or the apex is sore to touch This symptom is very difficult to explain The pain may also be dull

Palpitation This complaint is also very common and of the same type as that discussed in the other neuroses Like the dyspnea and pain it occurs often at rest and is particularly annoying The cardiac rate may be slow Many patients are distressed by palpitation and precordial pain when lying on the left side Since the same complaint occurs in about 30 per cent of normal people it is usually easy to reassure the patient as to its benign nature

Wood found dyspnea in 93 per cent fatigue in 88 per cent and sweating in 80 per cent of the subjects Nervousness was noted in 79 per cent and dizziness as well as pain in 78 per cent

Additional Complaints Many patients tend to perspire profusely This is very annoying if the hands are affected for these parts feel cold and clammy Some patients perspire on the least mental or physical effort Headache dizziness trembling and irritability are added complaints Some patients also mention blurring of vision numbness of the extremities loss of memory and inability to reach decisions

Signs

The hands are often blue (stagnant anoxemia) there is hyperpnea and the knee jerks are exaggerated

Cardiac hypermotility is easily found on palpation of the precordial area The heart beat is often accelerated and rates exceeding 120 at rest may be found usually the heart slows during sleep Physiologic systolic murmurs may be heard The first heart sound is loud at the apex Sometimes the blood pressure is elevated to 150/90 mm Hg or more (anxiety hypertension) presumably as the result of cardiac hypermotility The diastolic blood pressure may be normal even if the systolic pressure is markedly elevated (Hill and DeWar) The heart is always normal in size and shape if no unrelated complications exist Often x ray examination discloses a moderately dilated aorta This is a dynamic dilatation as in hyperthyroidism and the hypermotility of the left ventricle which expel it

stroke volume with greater force into the ascending aorta is largely responsible for this finding

Electrocardiographic findings have been described but they are equivocal and do not aid in the diagnosis

Many of these patients have a spastic colon and gastric hyperacidity A mild elevation of temperature is common and may be misleading

Etiology

The cause of the syndrome is unknown Stress is often a precipitating factor In some cases great nervous strain physical overexertion an exhausting illness or an infectious disease antedate the onset of neurocirculatory asthenia Emotional conflicts play a great role and explain the increased frequency of this syndrome in wartime It is found not only in cowards but also in men with a keen sense of duty Heredity is important for the family history is positive in approximately 50 per cent of the occurrence of psychiatric cases The imbalance of the autonomic nervous system is attributed by some to a central disorder The hypothalamic region has been suspected as the possible site of the lesion

According to Wood the symptoms resemble those of fear more than those of effort The mechanism is one of central stimulation The symptoms are the same as those observed in situations provoking anxiety and alarm It is an emotional reaction pattern peculiar to psychopathic personalities and subjects with almost any type of psychoneurosis

Prognosis

The syndrome is never dangerous to life and there are no serious complications Temporarily hyperventilation may cause tetany and even a condition like shock (hyperventilation syndrome) The extreme prostration may incapacitate the patient so much that months are spent in bed The outlook in respect to the duration of the syndrome depends upon many factors not the least of which is the correct management of the patient In the First World War 20 per cent of the patients recovered sufficiently for re entrance into general service 20 per cent were permanently unfit and the rest improved sufficiently to do light work The outlook for very advanced (stretcher) cases is poor A follow up study of more than 600 cases of the war of 1914—1918 revealed that 15 3 per cent of the patients recovered entirely 56 2 per cent remained stationary 3 2 per cent became worse and the rest improved (Grant) The death rate in these cases was no greater than in the general population but a remarkable number (22 cases) developed pulmonary tuberculosis

Differential Diagnosis

The distinction between neurocirculatory asthenia or cardiac neurosis and organic disease or extracardiac lesions sometimes offers great difficulties

A history of dyspnea a loud first sound over the apex and a systolic apical murmur may lead to the diagnosis of a rheumatic mitral disease It is easy to

rule out an advanced mitral lesion by x ray examination in the right oblique position this rule is not valid for early cases of mitral stenosis because in this instance the left atrium need not be enlarged

The increase of blood pressure the systolic murmur and the history of pain with typical radiation may suggest coronary disease with angina pectoris The differentiation between neurotic pain and atypical angina pectoris in coronary disease may meet with unsurmountable obstacles with the result that the final decision may have to be deferred for a while The appearance of pain with no relation to effort or excitement its prolonged duration or short stabbing character and the absence of any favorable response to nitroglycerin (therapeutic test) speak in favor of the neurotic pain and help in the differentiation It is noteworthy on the other hand that in coronary sclerosis a few hours or days before the full picture of coronary occlusion and myocardial infarction appears the attacks may also be atypical and may not even respond to nitroglycerin

In view of the paucity of objective signs malingering is not easily excluded

Hyperthyroidism is often suggested in these cases by virtue of the tremor the profuse perspiration the tachycardia and the cardiac hypermotility In neurocirculatory asthenia however there are no eye symptoms the basal metabolic rate is normal and the tachycardia disappears during sleep In both conditions the hands are moist but they are cold in neurocirculatory asthenia and warm in hyperthyroidism The condition may also be confused with brucellosis

The presence of slight temperature loss of weight and tachycardia may seem to indicate a beginning pulmonary tuberculosis Therefore a complete physical examination should be followed by roentgen examination of the lungs In this connection it should be recalled that temperatures of organic origin such as those of rheumatic fever tuberculosis and so forth are easily abolished by small doses (2 Gm daily) of aminopyrine (Pyramidon) The fever found in neurocirculatory asthenia or in hyperthyroidism is not modified by this drug but is lowered by opium derivatives

Experience during the recent war in particular has taught the importance of ruling out an early hypertension in these cases Blood pressures exceeding 150/90 mm Hg are common in neurocirculatory asthenia and only careful observation and the presence of hypertensive heart disease in one or both parents may permit the differentiation

Therapy

Not much help can be expected from drugs Small doses of chloral hydrate bromides or phenobarbital are useful and benzedrine has been recommended for the asthenia Tranquilizing agents seem to help Vitamins are given a tonics However medication prescribed is only for symptomatic treatment and does not cure the patient The less attention paid to the pulse rate and the heart once the diagnosis is established the easier it is to handle the situation

Of primary importance is psychotherapy with firm reassurance of the patient Fear should be removed if possible and the patient should be taught to readjust himself to his environment He should be taught to have a more philosophical attitude towards situations at home and in business Sometimes the help of a psychiatrist is needed but often the patient resists this advice for obvious reasons Much patience and much listening to the patient s complaints are necessary One often finds difficult life situations that cause emotional tension and here advice may be helpful The word neurosis is avoided The physician should never forget that a cardiac neurosis may have been initiated by an injudicious statement of a colleague Explanation of the nonorganic nature of the complaints does more good than mere reassurance Graduated exercises were in vogue for patients of this group during the First World War

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Chapter 27

Cardiac Diseases and Pregnancy

THE MOST COMMON HEART DISEASES of women in the childbearing age are rheumatic fever and *hypertension*. Congenital heart disease, cor pulmonale (particularly in kyphoscoliosis), or arteriosclerotic heart disease are less frequent.

The attitude of different physicians in many problems arising in these patients depends upon their background, experience, and education. Thus the gynecologist invariably speaks of pregnancy complicated by *cardiac involvement*, while the cardiologist talks about a cardiac disease complicated by pregnancy.

The responsibility a physician assumes in every decision is very great. He should never rely upon statistical results alone but should individualize each case on its own merits after thorough examination and observation. Statistics, however, as compiled in two monographs (Jones, Hamilton and Thomson), make the task easier and offer help in making the final decision. Unfortunately the attitude of many physicians confronted with the problems we are *about to discuss* often depends neither upon the experiences of others nor the known facts, but upon single recent personal observations.

Incidence. The incidence of rheumatic fever in pregnant women varies in different parts of the world but some idea of the importance of the problem can be obtained from the following figures.

In New England, the incidence of rheumatic heart disease among pregnant women is 1.5 per cent (Kellogg). In the Boston Lying In Hospital, 1.7 per cent of pregnant women were cardiacs (Hamilton and Thomson). In New York *rheumatic* heart disease was found in 2.6 per cent of pregnancies, while in Great *Britain*, 0.25 per cent of cardiac cases were detected among 20,306 deliveries (Donovan). Similar figures were recently obtained by Abramson and Tenney despite the lower incidence of rheumatic fever in the last few years. In all hospital statistics the number of cardiac patients is naturally higher than in the general population, since women with heart disease fortunately are referred to hospitals for observation and delivery in ever increasing numbers.

Heart disease ranks among the five most important causes of *maternal* death. It accounts for about 7 per cent of all *fatalities and claims* close to 1000 pregnant women a year in the United States.

Pathophysiology. Pregnancy increases the load for the heart, diminishes its reserve power and may cause decompensation in patients with organic heart disease. The work of labor magnifies this strain.

The circulating blood volume increases during pregnancy by 45 per cent beginning early in pregnancy and gradually reaching a maximum in the ninth lunar month There is a progressive increase in the plasma and total volume by 30 to 50 per cent A definite decrease occurs in the tenth lunar month and after delivery The red cell count hemoglobin percentage and hematocrit increase Because of the relatively greater increase of the plasma a relative anemia appears to be present The cardiac output is also increased about 50 per cent above normal in the latter stage of pregnancy It has been claimed that the placenta acts like an arteriovenous leak and that the circulatory adjustments in pregnancy may therefore be compared to those of patients with an arteriovenous fistula This is not proved The velocity of blood flow is increased The basal metabolic rate may rise up to 25 per cent (increased oxygen consumption of the fetus) Often the blood pressure rises slightly (Jensen) but more frequently it remains normal There is a marked retention of sodium probably due to a hypersecretion of aldosterone A peculiar disease of the myocardium which appears in the puerperium was described in the chapter on myocardial diseases (Sodeman)

The added demands of the placenta the greater weight of the patient the increased basal metabolic rate difficulties in respiration and certainly many other factors for the most part unknown at present increase the minute volume and the load on the heart The heart is anatomically larger during pregnancy (Tandler) The adverse effect of many aggravating factors gradually diminishes toward the end of pregnancy when lightening appears No available explanation is satisfactory for this phenomenon The circulatory disturbances mentioned begin to appear at about the twelfth week of pregnancy

Contraindications Frequently a certain valvular lesion is regarded as a contraindication to pregnancy Thus for many years mitral stenosis in any stage was considered particularly dangerous and few physicians hesitated to interrupt pregnancy in the presence of this lesion No less an observer than Mackenzie pointed out that mitral stenosis constituted a very common source of peril and most physicians of his time accepted the same view According to modern experience patients with mitral stenosis actually seem to offer a greater danger than those with other valvular lesions We are heartily in accord with this opinion Many other observers however regard aortic lesions as contraindications despite the fact that it is precisely in this lesion that full compensation is often maintained for many years

The presence of atrial fibrillation is considered by some authorities to be a bar to pregnancy while others emphasize correctly that it is not an added burden per se

The important question it seems to us is not *which* valvular lesion is present but how marked it is the extent of compensation the degree of functional capacity of the patient and the condition of the myocardium are of importance In this connection the four classes of functional capacity defined by the New York Heart Association according to the condition of the patient

are of great value in providing a better guide for the management of an individual case

Clinical Findings Cardiac examination of patients late in pregnancy reveals displacement of the heart due to the high position of the diaphragm This may lead to an erroneous diagnosis of cardiac dilatation A systolic murmur is audible (50 per cent) over the pulmonary artery and is explained by the kinking of this vessel (Landt and Benjamin) it disappears during deep inspiration The second pulmonic sound is often accentuated when the elevated diaphragm pushes the conus of the right ventricle closer to the chest wall The same mechanism may force the ascending aorta toward the chest wall in other cases and lead to an accentuation of the second aortic sound As a consequence of the cardiac displacement the electrocardiogram shows a deep Q wave in lead III in about 30 per cent of the cases

According to Mackenzie extrasystoles are very common and appear in about 50 per cent of healthy women during pregnancy Attacks of paroxysmal tachycardia in this period also have been repeatedly described These arrhythmias usually disappear shortly after delivery They are indicative of some change in the myocardium but the precise mechanism is unknown

Albuminuria is common and ankle edema due to pressure of the enlarged uterus on the iliac veins is also found often There is a low oncotic pressure A loud physiologic murmur in the presence of these findings may make it difficult to exclude an organic heart disease It is even harder to rule out beginning decompensation in a patient who is known to have an organic heart lesion In the presence of edema the status of the liver is important in excluding right ventricular failure but examination of this organ may be difficult in advanced pregnancy It is easy to diagnose left ventricular failure (pulmonary congestion) by the appearance of basal rales and a prolonged circulation time

Prognosis and Complications The heart disease may be so trifling that one need expect no risk from a pregnancy On the other hand it may be of such a degree that complications will develop with certainty The heart disease may be prohibitive In women over 35 years of age the danger of complications is particularly great

Dissecting aneurysms occur in pregnant women Spontaneous abortions are rare in cardiac patients Irregular menstruation and early menopause are common

The greatest strain on the heart occurs when the pregnancy is 28 weeks old and for 24 hours after delivery

According to older observations one out of every five pregnant women with chronic rheumatic heart disease develops congestive heart failure for the most part in the seventh or eighth month of pregnancy If decompensation appears there is an even chance of going through the term without difficulty There is no doubt that the danger of pregnancy in chronic heart disease was often overemphasized and that modern methods afford a much greater opportunity for cardiac patients to deliver a healthy baby without endangering their lives According to Hamilton the mortality of patients with compensated cardiac

lesions is 2 5 per cent Those which he places in his unfavorable group have a mortality of 16 7 per cent and the mortality in patients with atrial fibrillation is 33 per cent The death rate in patients with pregnancy and heart disease has fallen in recent years from 8—10 per cent to 2—3 per cent (Jensen Gordon) There is however always a great deal of uncertainty which precludes any dogmatism One of us observed a patient with a moderately advanced but compensated mitral stenosis who went through 12 normal deliveries without medical supervision We have also seen other patients with so mild a mitral stenosis that they were unaware of its existence and yet died immediately after delivery from a fulminating pulmonary edema

It is always helpful to know how previous pregnancies were tolerated If decompensation developed in a previous pregnancy in all probability a second pregnancy will lead to serious complications

Pulmonary edema may appear at any stage of pregnancy in mitral stenosis although the valvular lesion seems slight Help may come too late even if expert therapy is prescribed

The development of pulmonary edema during delivery or a few hours post partum is a dramatic and very serious complication particularly in patients with mitral stenosis Acute pulmonary congestion caused by strain during delivery and overfilling of the lesser circuit with blood returning in huge quantities from the pelvic veins are responsible for this dangerous complication We have not encountered it since we advised the obstetrician to administer morphine for the first 12 hours post partum to every woman with heart disease and suggested a phlebotomy in those patients whose delivery is more or less bloodless

Prolonged labor shold be avoided by all available means

Another serious complication is the development of subacute bacterial endocarditis following delivery One per cent of cardiac patients in a large series of carefully observed cases developed this complication To avoid this tragic event we advise 600 000 units of procaine penicillin daily for five days following delivery Some authors recommend also the intramuscular injection of streptomycin

It has often been maintained that cardiac patients whose pregnancy goes to term without complication and ends in a normal delivery afterward do not feel as well and their ability to work diminishes Some statistics show however that one or two pregnancies are often tolerated well without detriment to health and without shortening life Frequent pregnancies at intervals of one or two years are however dangerous Here also an evaluation of each patient is necessary in determining the course

Medical Advice In the evaluation of every case the age of the patient the degree of the lesion the status of the myocardium the functional capacity of the heart the reserve power and the history of previous failure must be considered

If a woman with organic cardiac disease asks whether she dare take the risk of pregnancy the answer must be no in the presence of congestive heart

failure even if earlier congestive heart failure was present and is now prevented by continuous medication There are patients in this group who reach term and contrary to all expectations have a normal delivery but they are exceptional The statement that delivery is shortened in decompensated patients owing to edema of the tissues remains unconfirmed

In the presence of a fully compensated valvular lesion the patient must be informed about the increased risk involved in pregnancy but in most instances she is willing to undertake it Continuous observation during the pregnancy is necessary beginning with the sixth lunar month the patient must be examined weekly for evidence of heart failure Activities must be reduced periods of rest must be prolonged the nutrition must be adequate and an ample supply of thiamine chloride and iron should be given Lack of thiamine is a common reason for cardiac symptoms and signs in pregnant women Sodium intake may have to be restricted

Valvulotomy in mitral stenosis has been performed successfully during pregnancy Often the operation is better performed after pregnancy terminates

There is no need for and no help can be expected from the prophylactic administration of digitalis before decompensation occurs At term the safest method of delivery is elected and strain should be avoided Until recently caesarian section under ether anesthesia was considered advantageous The patient was thus spared the work of delivery the danger of subacute bacterial endocarditis was reduced to a minimum the most favorable moment for the termination of pregnancy with the patient in the optimal state could be chosen if necessary the duration of the pregnancy could be shortened and sterilization could easily be included in the operation if this were desirable In patients with coronary sclerosis caesarian section is still preferred Many obstetricians are now against a caesarian section in rheumatic heart disease since the mortality of patients in whom surgery has been performed is a little greater but these cases usually have been more seriously ill It has been shown in a large series of observations that the dangers of delivery at term for the well prepared patient were grossly exaggerated This trend away from caesarian section may change however with new methods of preventing complications (antibiotics and anticoagulants which prevent infection thrombosis and pulmonary embolism)

Pitressin and ergotamine preparations are best avoided

How great the accomplishments of modern management of pregnancy in cardiac patients can be is illustrated by the following two sets of statistics collected in the pre penicillin era

In a series of 1089 patients in whom pregnancy was complicated by rheumatic heart disease the total mortality was 1 per cent and the cardiac mortality was only 0 17 per cent (Mendelson) In a series of 43 cases in which there was cardiac involvement but a spontaneous delivery and 18 cases of caesarian section there was no mortality (Frey and Lardi)

If the patient is seen for the first time in the early weeks of pregnancy (the first three lunar months) with signs of decompensation therapeutic abortion is indicated Religious principles must be considered the situation must be explained to the patient and her family and the decision must be made by them It has also been recommended that the patient be sterilized at the same time if decompensation begins in the first five months of pregnancy These operations are of course performed after the cardiac status is improved as far as possible by the usual treatment

If decompensation starts after the fifth month it is advisable to wait for delivery at term and to keep the patient under continuous close observation and treatment Physical and mental rest and sodium free diet are usually required Digitalis and mercurial diuretics are not harmful Lactation is permitted if no congestive failure exists Often a marked improvement occurs in the last weeks of pregnancy when the load on the heart is reduced and the risks are no greater than with an operative procedure In the opinion of many obstetricians section is indicated only when there are definite obstetrical indications for it The first stage of delivery is shortened and the use of an analgesic or ether low spinal caudal anesthesia is recommended whereas at full dilation the application of a low forceps shortens the second stage

While the blood pressure in the healthy woman scarcely changes during pregnancy patients with essential hypertension show an increase of pressure There is also evidence of impairment of kidney function Persistent increase of blood pressure to values over 200 mm Hg from the beginning are indications for an interruption of pregnancy For some a diastolic blood pressure over 100 mm Hg is an indication for interruption of an early pregnancy Infant mortality is high in these cases The danger of toxemia of pregnancy is great with papilledema albuminuria and headache According to Browne and Dodd a blood pressure of 150/100 mm Hg at the beginning of pregnancy gives little likelihood of a successful pregnancy for birth of a viable child the chances are no better than 32 per cent Gain in weight albuminuria edema and increase of blood pressure are early signs of toxemia usually occurring after the twenty fourth week of pregnancy Patients with essential hypertension before pregnancy are often worse off after pregnancy

According to others patients with moderate hypertension and even chronic nephritis tolerate pregnancy well when azotemia is absent Myocardial infarction is compatible with a normal course of the pregnancy provided it does not occur at the end of the term

Patients with a noncyanotic *congenital heart lesion* seem to tolerate pregnancy relatively well In patients with patent septa or a patent ductus arteriosus as well as pulmonary stenosis pregnancy is as a rule tolerated well In patients with mitral stenosis hemoptysis or pulmonary edema may occur only during pregnancy and disappear completely afterward

Patients with atrial septal defects usually stand pregnancy very well In patients with aortic coarctation the danger of aortic dissection is great

A marked bradycardia often appears normally for the first few days following delivery

If paroxysmal tachycardia appears therapy with quinidine and procaine amide is permissible in spite of the pregnancy

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Chapter 28

Cardiac Disease and Surgery

PATIENTS AS A RULE tolerate major surgical procedures strikingly well despite the presence of advanced cardiac alterations This is particularly true if congestive heart failure is absent Anxiety about patients in this group often turns out to be unjustified

Since there are dangers inherent in every operation and the hazards of pulmonary embolism in particular are greater in patients with a disturbed circulatory system operations should be restricted to those absolutely indicated If for example roentgen therapy promises the same success one should not operate A repair of a hernia or the replacement of a prolapsed uterus may be omitted and conservative treatment advocated

While the operative mortality was 1 9 per cent in patients without heart disease who underwent a prostatectomy it was three times as great in cardiac patients (Iversen et al) Others found that in coronary sclerosis the mortality increased four times In such patients it has been recommended that nitroglycerin tablets be inserted sublingually several times during the operation (Morrison)

In 257 patients whose ages varied from 35 to 83 12 4 per cent of whom had survived a previous coronary thrombosis the postoperative mortality from cardiac accidents was 4 3 per cent (11 cases) among the 11 mortalities coronary thrombosis occurred postoperatively in seven (Brumm and Willius) Ltsen and Proger found in 517 patients with coronary disease a postoperative mortality from all causes of 2 9 per cent The mortality was only 2 per cent in 4154 patients without clinical evidence of heart disease Two of 11 patients with acute myocardial infarction who needed emergency operations died In such case the mortality seems to be definitely higher

With skillful operation and expert anesthesia cardiac strain is not increased (Marvin) Selection of the wrong anesthetic anoxia or otherwise badly conducted anesthesia poor postoperative management as exemplified by the intravenous administration of excessive amounts of fluid may do great harm

In coronary sclerosis the danger of coronary thrombosis is great and this danger is augmented by fall of blood pressure or shock Shock irrespective of its origin is often responsible for multiple arterial occlusions in elderly patients with coronary sclerosis According to some statistics the mortality in patients with healed myocardial infarction is higher than in other cardiacs (Butler et al) on the other hand experience shows that such patients tolerated thyroidectomy astonishingly well when this operation was frequently performed in cardiac

patients The same situation prevails in patients requiring a prostatectomy The heart is strained by hemorrhage large intravenous infusions hypoxia and tachycardia Deliberate lowering of blood pressure by the anesthetist should be avoided

Patients with valvular lesions tolerate surgery very well Atrial fibrillation is no contraindication especially when it accompanies a valvular lesion and not coronary sclerosis Digitalization is important in these patients

Myocardial lesions undoubtedly increase the danger but fortunately primary myocardial lesions are uncommon

The selection of the correct anesthetic is very important Inhalation anesthesia with ether seems most preferable Ether does not damage the heart muscle and has no appreciable influence on blood pressure It practically never causes arrhythmias It paralyzes the peripheral vagus apparatus and thus diminishes the danger of asystole Oxygen should be admixed in ample amounts It is well *however to avoid ether if pulmonary complications are present*

Ethylene and nitrous oxide are permissible if care is taken to supply sufficient oxygen Ethyl chloride is however known to provoke ventricular fibrillation Cyclopropane anesthesia otherwise very satisfactory should be used in cardiac patients only with great caution since the heart dilates markedly during its *administration (Brace et al) Cyclopropane also causes multiple extrasystoles* although they are less dangerous than those encountered in chloroform anesthesia While some investigators have noted extrasystolic arrhythmias and tachycardias in 10 per cent of anesthesias with cyclopropane ventricular fibrillation is rare Opinions about the origin of these arrhythmias vary and no explanation is completely satisfactory

Spinal anesthesia invites the danger of a sudden fall of blood pressure particularly in hypertensive patients The anesthetist must do everything to prevent hypoxia and a fall of blood pressure and must avoid the administration of adrenalin or pituitary extracts

Loss of electrolytes (potassium) is an important reason for postoperative heart failure

Intravenous administration of barbiturates is to be avoided in patients with a damaged or overdilated heart muscle Barbiturates serve in the animal experiment as preferred compounds for inducing myocardial damage

Because of the presence of hypoxia nitrous oxide should be avoided in patients with coronary disease

Consideration should be given to the fact that excessively rapid absorption of local anesthetics may be dangerous for the heart The admixture of epinephrine to prevent rapid absorption should be avoided in patients with organic heart disease It may be replaced by preparations of the pituitary

The question of cardiac preparation preliminary to operation has been widely discussed Water retention should be abolished as much as possible and anemia corrected *Positive evidence* of the advantage of a prophylactic digitalization is not available and preparation of the patient by this method has been abandoned If a patient requires an emergency operation and shows evidence of

decompensation or a very fast ventricular rate with atrial fibrillation much can be accomplished with an injection of strophanthin or one of the pure glycosides (digoxin cedilanid) while preparations for the operation are completed Emergency operations must be performed regardless of the cardiac status of the patient

Cardiac arrest (via reflexes) is an operative complication which is reported more frequently at present Immediate opening of the chest (fourth intercostal space) and cardiac massage are necessary within three minutes (p 581) External electrical stimulation of the heart may suffice

At present, surgeons are generally inclined to favor early postoperative ambulation We agree with this measure but believe it should be done with care since newly formed thrombi are easily dislodged Blodgett and Beattie found the incidence of deep vein thrombosis even somewhat higher in patients who were made active at an early stage

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Chapter 29

Disturbances of Cardiac Rhythm

Clinical Aspects of Extrasystoles

THE DISTURBANCE OF CARDIAC RHYTHM caused by extrasystoles (premature beats) has been known ever since the human pulse was felt Until the end of the last century however the chief cause of the intermittent pulse was unrecognized despite the fact that after the work of Marey extrasystoles were induced very often experimentally to aid in the study of fundamental questions of cardiac physiology After the similarity between premature contractions caused in animals by mechanical or electrical stimuli and those appearing in man was recognized by Wenckebach and Cushny this disturbance was found to be the most common cause of cardiac irregularity

Definition Extrasystoles are premature contractions interrupting cardiac rhythm caused by the preceding beat they are coupled to this beat by an interval which is usually short and constant for a given case By this definition premature beats caused by other mechanisms (parasystole or interference dissociation) are excluded

Origin and Appearance While they may originate in any part of the heart two main groups are distinguished atrial and ventricular extrasystoles In rare cases extrasystoles originate in the sinus or in the atrioventricular node For practical clinical purposes it is immaterial from what part of the atrium or ventricle the extrasystole emerges

Extrasystoles may appear singly with a long chain of normal beats between them or they may occur frequently after every few beats or even after every sinus beat In the last case we speak of bigeminal rhythm if two extrasystoles follow each normal beat regularly a trigeminal rhythm exists Many authors incorrectly call the appearance of one extrasystole after two normal beats a trigeminus

All variations and combinations occur If several extrasystoles follow each other we speak of groups of extrasystoles if the chain is longer we may call it a short paroxysmal tachycardia

Electrocardiogram Figure 92 shows three premature atrial contractions which interrupt a regular sinus rhythm They are represented in the electrocardiogram by premature and slightly different looking P waves the atrial extrasystoles are conducted normally to the ventricle

A ventricular bigeminal rhythm is present in figure 93 This tracing was obtained from a 50 year old man who had no evidence of cardiac disease Each normal beat is followed by a ventricular extrasystole

In figure 94 series of ventricular extrasystoles are visible These extrasystoles appeared in a case of rheumatic fever The atrioventricular conduction time in this case is prolonged to 0 26 second



FIG 92 Three atrial extrasystoles

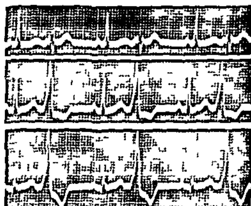


FIG 93 Ventricular extrasystoles in the form of a bigeminal rhythm

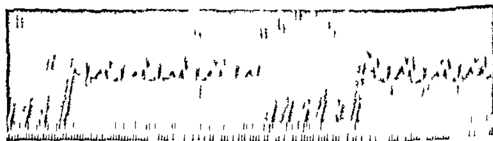


FIG 94 Prolonged atrioventricular conduction time and a series of ventricular extrasystoles

Cardiodynamics Every extrasystole causes a considerable disturbance in cardiodynamics An extrasystole may occur so early in diastole that ventricular filling is negligible The more prematurely an extrasystole appears the smaller is the stroke volume of the extrasystolic contraction and the smaller will be the pulse caused by it If extrasystoles are very premature no pulse is palpable in the peripheral arteries and the contraction is abortive Such an extrasystole advances

little or no blood into the arterial system at the same time during the extra systolic contraction the inflow of blood from the atria into the ventricle is impeded and venous stasis develops Since the postextrasystolic pause is as a rule much longer than the normal cardiac pause of the individual the stroke volume of the first normal beat following the extrasystole is correspondingly larger and the associated pulse stronger Whereas an extrasystole propels too little blood into the arterial system the situation is balanced by the first normal beat after the

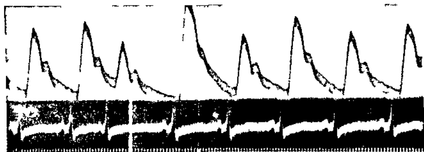


FIG 95 Pulse changes typical of extrasystoles (see text)

extrasystole and circulatory disturbance is prevented The minute volume remains normal even if some of the systoles (extrasystoles) eject little blood into the arteries Thus a patient may have many extrasystoles per minute for a lifetime and still not suffer from any disturbance of the circulation

In figure 95 the pulse tracing and the electrocardiogram of a patient with atrial extrasystoles are reproduced An atrial extrasystole appears after the second normal beat The extrasystole causes a premature smaller pulse wave Due to the postextrasystolic pause the first postextrasystolic pulse wave is much larger An alternating pulse is visible for the first few postextrasystolic beats

Symptoms Most extrasystoles provoke no sensation Patients are frequently encountered in whom multiple extrasystoles or bigeminal rhythm have persisted for months or years without attracting attention or causing any symptoms In other instances the attention of the patient is directed to the disturbance accidentally by the awareness of an irregular cardiac rhythm in the stillness of the night when one ear rests upon the pillow through the palpation of the pulse or through the remark of a physician Under these circumstances the patient notices the irregularity but otherwise he does not feel it

At times extrasystoles create considerable annoyance The symptoms vary Rarely the extracontraction itself is felt as an unpleasant impact Patients often give very vivid descriptions of their sensations so that the diagnosis can be made on the basis of the history Some report a sensation like a sudden blow others a brief awareness of some event in the cardiac area which is described differently according to imagination and education It is a sudden jumping kicking or a sudden blow or somersault Sometimes it is referred to as a skipping of the

heart other times a sudden sharp painful sensation is felt In neurotic patients who observe the heart and the sensations in the cardiac area carefully a pain may be felt with every extrasystole which makes the whole body twist as if the patient had touched a live wire Slight faintness may also appear Frequently the pauses after the extrasystole are perceived unpleasantly the patient has the sensation that his heart suddenly stood still He anxiously waits to see 'whether it will begin to beat again' This sensation is interesting in view of the shortness of the postextrasystolic pause Most often however the normal beat after the extrasystole is felt as a strong contraction and produces the sensation described above This is natural since the first normal beat after the extrasystole expels a very large stroke volume In aortic regurgitation with a large left ventricle and a larger stroke volume even with regular cardiac action the postextrasystolic beat is particularly unpleasant

Of interest is the dry short cough caused by an autonomic reflex occuring in some persons with every extrasystole

Signs If the existing rhythm is interrupted by premature beats which are followed by a long pause the correct diagnosis can be made in most cases without an electrocardiogram The earlier the extrasystole occurs and the more incomplete the filling of the ventricles the louder is the first heart sound particularly over the apex Owing to the small stroke volume the second heart sound is soft When extrasystoles occur very early the second heart sound may be absent since the semilunar valves are not opened by the abortive systole

Not rarely extrasystoles disappear at the time of the examination They may vanish with any measure which increases the heart rate and consequently shortens the length of diastole Therefore exertion and excitement

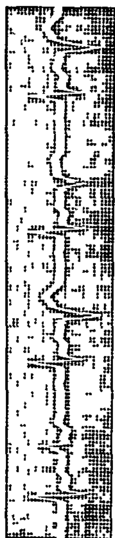


FIG 96

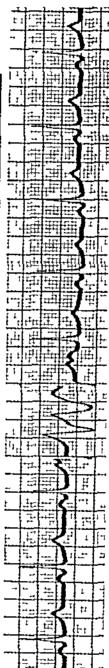


FIG 97 →

FIG 96 Multiform ventricular extrasystoles

FIG 97 Series of multiform extrasystoles in a patient with coronary sclerosis death occurred suddenly one day after this tracing had been taken This type of extrasystoles not rarely precedes ventricular fibrillation

usually abolish extrasystoles Often they appear however a short time after exertion when the initial tachycardia subsides Sometimes they are elicited by carotid pressure or after inhalation of amyl nitrite (Scherf)

Differential Diagnosis In a majority of cases the occurrence of a premature contraction disturbing the existing rhythm with a succeeding long pause permits the diagnosis without graphic registration Under certain conditions however difficulties arise

If extrasystoles are multiple and occur irregularly they may be confused with atrial fibrillation The differentiation will be discussed later

In patients with a continuous bigeminal rhythm in which the first sound of the extra contraction alone is heard gallop rhythm is occasionally diagnosed because a third heart sound is heard shortly after the two normal sounds Since extrasystoles usually disappear on acceleration of the heart any slight exertion — sitting up and lying down a few times — will abolish the extrasystoles this exercise will usually accentuate the gallop rhythm

Occurrence Extrasystoles may appear at any age Repeatedly they have been detected during auscultation of the fetal heart sounds (Antoine) Most physicians believe that there is rarely a healthy individual who has never exhibited an extrasystole They come and go without detectable reason and are in most cases devoid of any importance

In other instances definite reasons for their occurrence can be found In one individual they appear with meteorism or constipation in another with deep breathing In one patient they are found only on deep inspiration in another only with deep expiration They may occur only before menstruation and are a common event during pregnancy For the most part they are present only at rest but in rare instances they appear during or immediately after exertion

Certain drugs and certain substances like caffeine and nicotine may cause them The extrasystoles due to drinking strong coffee and after smoking have been known for many years and were discussed even at the time when one spoke only of an intermittent pulse Chloroform and cyclopropane anesthesia often elicit extrasystoles Premature contractions are also not rare following an injection of adrenalin and allied substances One of the more important types of clinical extrasystoles is the variety that appears during treatment with digitalis

Extrasystoles are occasionally caused by reflexes That premature contractions may be elicited by carotid pressure or on deep breathing was mentioned above The literature on extrasystoles caused by mechanical or chemical irritation of the respiratory tract or from the digestive tract is large Extrasystoles appear on distention of the stomach (Pribram and Mayer) on the insertion of a tracheal tube during cyclopropane anesthesia (Reid and Brace) in patients with gall bladder disease and in those with a hiatus hernia (Kaestner) Certain hypothalamic centers have been shown to be an important link in these reflexes (Allen Brown et al)

If extrasystoles appear during diphtheria coronary disease pneumonia or scarlet fever they often indicate a lesion of the myocardium and have diagnostic

importance Extrasystoles due to an organic heart disease often but not invariably are recognized electrocardiographically by the fact that they seem to arise from multiple foci

Extrasystoles have been described in allergic reactions (Harkavy)

Extrasystoles may persist for many years in the same individual Walsh observed them on himself for 40 years

Mechanism The finer mechanism of origin of extrasystoles is still unknown in spite of the ease with which they can be elicited by mechanical electrical or chemical stimuli

Extrasystoles are caused by different disturbances In rare cases a circus movement or re entry mechanism is active In a majority of cases however firing of an impulse in an abnormal focus initiated by the beat preceding the extra systole takes place (Scherf and Schott)

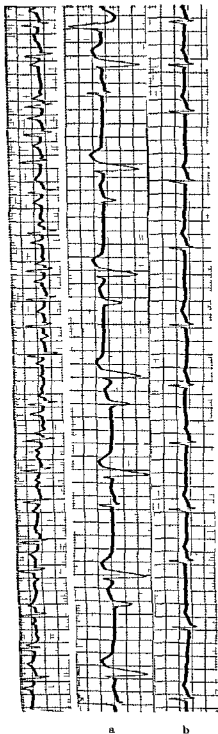
Clinical Importance While extrasystoles arise from an abnormal type of stimulus formation it is incorrect to assume the presence of cardiac disease simply because extrasystoles exist There are many arguments to support the assumption that the abnormal stimulus formation takes place in one fiber a center It is easy to conceive that the structure of the cell in one of the innumerable muscle fibers becomes altered leading to an abnormal depolarization of this cell and to a premature contraction Indeed one may assume that frequently in other organs of the body a single cell may be abnormal in a similar way without the organ to which it belongs being diseased But such an abnormality is rarely recognizable in other organs In the heart however if a stimulus formed by an abnormal center is above threshold it may excite first the neighboring cells and then the entire heart thereby being easily detected

If extrasystoles occur the only deduction permissible at first is the presence of a disturbance in a restricted area This disturbance is probably limited to a single cell If the remainder of the heart shows nothing abnormal — no anginal pain or infectious disease i e no condition in which cardiac damage is suspected — then the extrasystoles are usually devoid of any significance In the appraisal of the case it is immaterial whether few or many extrasystoles are present

Since extrasystoles may constitute even an early sign of a pathologic process in the myocardium every patient in whom premature contractions are found deserves a careful examination If no abnormalities are discovered he should be observed over a period of time In some cases only prolonged observation permits one to decide whether a purely local and negligible alteration exists or whether the extrasystoles indicate the development of a cardiac disease which otherwise would have escaped detection

If the physician is consulted by a patient who reports that extrasystoles have been present for years the negative result of even a single thorough examination will be sufficient to show that a harmless disturbance exists in a person with a healthy heart

Most extrasystoles have no prognostic significance for prognosis depends upon the cardiac status



a b

FIG 98 FIG 99

Multifocal ventricular extrasystoles always indicate myocardial damage and are therefore a finding of importance (figures 96 and 97)

Figure 96 shows an instance of multiform extrasystoles in lead II This tracing was taken from a 61 year old man with coronary sclerosis and angina pectoris The atrioventricular conduction time is prolonged to 0 26 second The width of the QRS complex is 0 12 second and the T waves are inverted Each sinus beat is followed by a ventricular extrasystole but their form continually varies The extrasystoles seen in healthy people always have the same form even if they persist for years

In an overwhelming number of cases unifocal extrasystoles are harmless but they may also accompany myocardial disease In conditions in which atrial fibrillation is common such as mitral stenosis hyperthyroidism and coronary sclerosis atrial extrasystoles may precede the onset of fibrillation for some time

A typical disturbance appearing in any age but found especially often in elderly patients is the arrhythmia shown in figure 98 Atrial extrasystoles originating in many foci and shifting of the pacemaker with varying forms of T waves are seen This arrhythmia often precedes atrial fibrillation

Treatment If an individual does not feel the extrasystoles and if examination as well as observation reveals a healthy heart it is a serious mistake to draw the attention of the

FIG 98 Shifting pacemaker and multiform atrial extrasystoles

FIG 99 Multiform ventricular extrasystoles partly bound to ectopic idioventricular beats in a 67 year old patient under treatment with digitalis (a) Following the administration of 5 grams of potassium chloride the extrasystoles disappeared (b)

patient to the cardiac irregularity or to treat it The layman is readily inclined to consider any irregularity of the ever constant rhythm of the heart as a serious disease

If a healthy individual consults the physician because he feels the extrasystoles and the examination reveals no cardiac disease the harmlessness of the disturbance should be explained to the patient and an endeavor made to convince him that he may lead a completely normal life It is well to point out that this disturbance occurs chiefly at rest while physical exertion which precipitates symptoms in organic heart disease causes no discomfort and as a matter of fact usually abolishes the extrasystoles

If the physician omits explanations or if he lacks the necessary knowledge and authority for this purpose indeed if he speaks of a mild heart muscle irritation and suggests restriction in some activities the patient simply sees his own conception of an organic heart ailment thoroughly confirmed He observes himself more carefully and with greater anxiety counts the number of premature contractions per minute observing all the details of the sensations caused by them The anxiety neurosis which soon develops from a harmless phenomenon can be treated only with difficulty and patience If the physician succeeds in convincing the patient that the extrasystoles are meaningless they are usually soon disregarded This is accomplished more readily if the physician insists authoritatively that the patient is a healthy person and should lead the life of a normal individual Nothing will convince the patient so readily of the innocence of his disturbance as lack of prohibitions and restrictions Furthermore the patient should be instructed not to watch the rate or rhythm of his pulse

The result of this therapy depends upon whether or not the patient can be convinced that the extrasystoles are meaningless and that they can be dismissed as unimportant

If they occur in organic heart disease the extrasystoles per se rarely require drug therapy Exceptions are extrasystoles in coronary thrombosis which may be precursors of ventricular fibrillation and the previously mentioned extrasystoles in diseases that are often accompanied by atrial fibrillation

If definite factors are found to release extrasystoles an attempt should be made to eliminate them Often the correction of marked meteorism a high diaphragm a severe constipation and gall bladder disease or cessation of smoking will permanently abolish the extrasystoles

Treatment with drugs is not necessary in most cases Such therapy affords relief only for the duration of administration As soon as the patient discontinues treatment the extrasystoles recur and the patient becomes more upset than before

In addition to the conditions mentioned earlier the administration of drugs is indicated when the extrasystoles multiply in a threatening manner or evoke so many unpleasant complaints that it seems advisable to remove them at least temporarily in order to convince the patient that palliative treatment and control of his condition is possible It is however advisable to inform the patient before instituting treatment that extrasystoles will probably recur when the administration of the remedy is stopped

Since Wenckebach s recommendation quinine and its much stronger isomer quinidine (Frey) are regarded as the most effective remedies for abolishing extrasystoles because they diminish the irritability of the heart and depress stimulus formation and conductivity If suitable doses of these drugs are administered extrasystoles are abolished in most instances

Since quinidine is rapidly eliminated from the body it is advisable to give small doses frequently As with all forms of cardiac therapy the opportunity to watch the success of the treatment permits adjustment of the therapy to the needs of the patients A capsule or tablet containing 0 2 Gm of quinidine sulfate is prescribed and the patient is advised to take it four or five times a day The first dose should be given as early as possible in the morning the last is given late in the evening If these doses do not suffice the single doses are increased until *the extrasystoles disappear*

A second remedy that removes extrasystoles regularly is digitalis It may seem strange that a drug which frequently produces extrasystoles should also be employed to abolish them It happens however that extrasystoles appear during digitalis therapy only under specific conditions (see digitalis therapy) As a matter of fact practically every substance which causes extrasystoles in certain doses may abolish them in others This is true for example with potassium magnesium procaine and even quinidine The extrasystoles which are not the consequence of digitalis disappear during digitalis treatment Often small doses such as 0 2 Gm daily for four or five days suffice for this purpose One disadvantage of this procedure is that many patients knowing that digitalis is given for heart disease become frightened when this remedy is mentioned It is however rarely necessary to prescribe digitalis to abolish extrasystoles A rare indication is multiple extrasystoles requiring drug treatment and at the same time the presence of idiosyncrasy of the patient to quinidine

In recent years procaine amide (Pronestyl) has been introduced into the therapy of cardiac arrhythmias It can be given orally and is not rapidly destroyed by enzymes as is procaine The dose is 0 50—0 75 Gm three or four times daily Quinidine should remain the drug of choice Pronestyl more useful in ventricular than atrial extrasystoles is given when hypersensitivity prevents administration of quinidine The doses of Pronestyl required for the treatment of extrasystoles and paroxysmal tachycardia are three times as large as those of quinidine (Schaffer) The side effects of both compounds are similar

Often it is possible to abolish extrasystoles particularly those due to digitalis with potassium salts given orally (figure 99) This treatment has considerable interest and will be discussed in the chapter on paroxysmal tachycardia

CLINICAL ASPECTS OF ATRIAL FIBRILLATION AND ATRIAL FLUTTER

Atrial Fibrillation

Atrial fibrillation was known for a long time to those who performed animal experiments Formerly the condition was called arrhythmia perpetua before it

was realized that the irregularity may disappear spontaneously or be abolished by treatment Total disorder of the cardiac rhythm in clinical atrial fibrillation was recognized as delirium cordis by physicians of the last century The identity of both was suggested by Cushny and Edmunds but it was not proved until the introduction of electrocardiographs in institutions (Rothberger and Winterberg as well as Lewis)

Incidence Atrial fibrillation is present in approximately 50 per cent of patients who seek hospitalization because of cardiac diseases It is very common in rheumatic mitral lesions in hyperthyroidism and in coronary sclerosis But fibrillation may also occur in other valvular diseases as well as in myocardial lesions and hypertension It is not an unusual complication of diseases frequently accompanied by myocarditis such as pneumonia and typhoid fever but it is rather rare in patients with syphilitic aortitis and syphilitic aortic regurgitation Although uncommon in cor pulmonale and bacterial endocarditis every cardiologist has observed it in these conditions

Atrial fibrillation has been observed in an infant three months old (Coldbloom and Segall) It is occasionally seen in otherwise apparently healthy persons after violent exercise

Occasionally atrial fibrillation is discovered in a patient whose heart has been completely normal through decades of careful observation In some of these patients some latent cardiac pathology myocarditis accompanying streptococcic infection for instance might have existed and have escaped detection while the fibrillation persisted

Electrocardiogram Figure 100 shows a typical instance of atrial fibrillation in the 3 standard leads The tracing was obtained from a 61 year old man with coronary sclerosis The irregularity of the ventricular activity is clearly visible Characteristic however are the irregularly formed fibrillation waves (F waves) which replace the normal P waves

Dynamics Patients with atrial fibrillation in whom less than 80 atrial stimuli per minute reach the ventricles due to a high vagal tonus or slow conductivity of the specific tissue feel normal If the heart of these patients is otherwise normal the fibrillation is asymptomatic and is discovered only by chance Occasionally one even sees patients with organic heart disease — for instance a slight rheumatic mitral stenosis — *who alternate between fibrillation and sinus rhythm without being aware of the difference*

Unfortunately these cases represent the exception As a rule the conduction system transmits more than 80 stimuli per minute to the ventricles and with faster rates symptoms increase The inadequate output and the fall of the minute volume associated with it lead to a feeling of weakness and faintness Dyspnea on exertion may appear but often is not prominent since the rapid activity of both right and left ventricles leads to venous and hepatic congestion i e to signs of right heart failure and not to pulmonary congestion In fact the appearance of right ventricular failure often coincides with the disappearance of any existing pulmonary congestion

The engorgement of the neck veins causes a sensation of fullness and constriction The enlargement of the liver leads to nausea as an early symptom and later to vomiting and right hypochondrial pain

The tachycardia may cause anginal pain especially if the patient has coronary sclerosis It may also cause fainting and other cerebral phenomena particularly in patients with cerebral vascular sclerosis Too rapid ventricular action in patients with atrial fibrillation may lead to Stokes Adams attacks and even to sudden death although the latter event is not unequivocally proved



FIG 100 Atrial fibrillation and the effect of digitalis on the RS T segments and T waves

Signs The complete disorder of the heart rhythm usually permits the diagnosis without difficulty If the ventricular rate is slow the arrhythmia is not so easily recognized but it becomes more apparent with prolonged auscultation A slight increase of the heart rate by moderate exertion brings out the arrhythmia more distinctly

With the appearance of atrial fibrillation and increase of the ventricular rate the blood pressure falls if venous pulsations are visible in the veins of the neck atrial waves are absent

Due to the prolonged tachycardia signs of congestive heart failure may appear even if the heart is otherwise healthy The high ventricular rate impairs cardiac blood supply and therefore leads to dilatation Relative mitral and tricuspid regurgitation may appear in an otherwise healthy heart if the fast ventricular rate in atrial fibrillation remains uncontrolled for a long time

Differential Diagnosis In most cases it is easy to make the diagnosis without resort to graphic methods The differentiation between multiple irregularly appearing extrasystoles and atrial fibrillation may be difficult In these cases

an exercise test or the inhalation of amyl nitrite permits differentiation since extrasystoles usually vanish if tachycardia shortens diastole and the heart rhythm temporarily becomes regular Under the same conditions the arrhythmia due to fibrillation becomes more obvious since now more stimuli are conducted to the ventricles With an arrhythmic heart action and a rate exceeding 120 atrial fibrillation is usually present

Sometimes respiratory arrhythmia is confused with atrial fibrillation particularly if the relation between the respiratory phases and the arrhythmia is somewhat atypical The disappearance of the arrhythmia when the patient holds his breath leads to the correct diagnosis

One often hears the remark that the patient fibrillated less today than on previous examinations This statement is incorrect The fibrillation in such cases remains unchanged but the ventricular rate is slower and the arrhythmia is less distinct

Mechanism Attempts to explain the abnormal mechanism causing atrial fibrillation on the basis of pathologic structural changes have been abandoned While it is true that the condition is common in some cardiac diseases and rare in others and abnormal histologic findings have been repeatedly described there is general agreement that atrial fibrillation is often an abnormal functional disturbance without anatomic alterations

For many years the opinion prevailed that atrial flutter and fibrillation are caused by a rapid circus movement of a central or mother wave in a closed path

It is impossible to discuss in this connection the fascinating and ingenious work that has been performed in order to explain this common disturbance The reader is advised to consult textbooks of electrocardiography or monographs on the subject to obtain such information

Recent investigations have shown that these arrhythmias can be explained better by a rapid stimulus formation in a center (Scherf et al) (figure 101) In atrial flutter one center forms the impulses while in fibrillation one or more centers are active (Scherf et al) There are still authors who maintain that atrial flutter and fibrillation are caused by a circus movement mechanism In flutter they would have to explain why it persists when the path around the venae cavae is interrupted by a broad ligature across the sinus node and the neighboring tissue (Scherf) In flutter and in fibrillation they would have to explain why cooling of the tip of the left atrial appendix on which aconitine had been applied in order to elicit them immediately stops these disturbances of rhythm and why they reappear when cooling is discontinued (Scherf et al)

Atrial (and ventricular) fibrillation may appear in a somewhat damaged heart the metabolic state of which is abnormal if one single stimulus falls in a certain period the so called critical or vulnerable period early in diastole At this time an electrical or a *light mechanical stimulus* — *simple touching* of the heart for example — or a natural stimulus in the form of a premature extrasystole initiates fibrillation It was pointed out before that in patients with mitral stenosis or hyperthyroidism atrial extrasystoles often precede atrial fibrillation It may

be assumed that one of the extra systoles occurred precisely during the vulnerable phase and set up the fibrillation During this vulnerable pha e a few hundredths of a second at the end of systole and at the onset of diastole one stimulus may lead to rapid firing of impulses

Important for the understanding of atrial fibrillation in mitral stenosis is the experience that under certain conditions stretch exerted on the right atrium may elicit this arrhythmia (figure 102)

Duration Attacks of atrial fibrillation last for variable periods Often a paroxysm persists only for a few hours while we have seen attacks last no longer than a few seconds In other cases the disturbance remains for months or years If attacks of atrial fibrillation recur frequently their management and clinical importance also depend upon the ventricular rate With higher rates they have the same importance as attacks of paroxysmal tachycardia

Treatment In slow fibrillation that is atrial fibrillation with a slow ventricular rate no special treatment is required To be sure such patients tolerate effort somewhat less than people with normal cardiac action because the increase of heart rate on exertion is usually greater Patients with atrial fibrillation are however often encountered who for many years show no other symptoms or signs

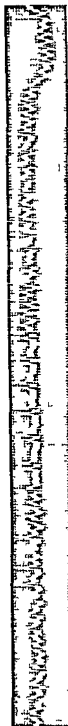


Fig 101 Dog experim nt Atrial fibrillation was create l by the application of crystalline aconitine on the appendix of the right atrium Cooling the ar a of application stopped the fibrillation and restored sinus rhythm (center of tracing) interruption of the cooling permitted the atrial fibrillation to reappear This result cannot be explained by the circus movement theory it speaks in favor of rapid firing off of impulses in a cent r



Fig 102 Atrial fibrillation had been induced in a dog in the same manner as described in figure 101 It disappeared after 56 minute Stretching the wall of the right atrial appendix leads to temporary reappearance of the fibrillation

The abnormal impulse formation in the atria during atrial fibrillation is of less importance than the ventricular rate — fibrillation is proportionately more harmful as the ventricular rate rises. Therefore, treatment is aimed chiefly at reducing the ventricular rate and keeping it low. With some exceptions (febrile disease, rheumatic fever, pulmonary embolism, hyperthyroidism) this is possible with the aid of digitalis. By increasing vagal tonus and thus inhibiting the atrioventricular conduction as well as by a direct action on the muscle fibers diminishing their conductivity, digitalis reduces the ventricular rate. The fibrillation in the atria proceeds uninfluenced. Rarely does it stop during the administration of digitalis. The treatment is easy to carry out and the results are good. Only in the above named conditions is a slow ventricular rate obtained with difficulty.

Since part of the action of digitalis is symptomatic in reducing the ventricular rate, the question is often asked whether it would not be wiser to abolish the fibrillation itself by means of quinidine. As a matter of fact, one can succeed in restoring sinus rhythm in 70 to 80 per cent of the cases by administration of quinidine sulfate. Nevertheless, the treatment is rarely used.

At first, some important contraindications must be considered. With long lasting fibrillation, mural thrombi may form in the atrial appendices and when powerful atrial contractions are again instituted upon the return of normal rhythm, these thrombi may be released and produce fatal embolism. Unfortunately, such accidents are not rare and are regrettable, since the administration of quinidine to patients with atrial fibrillation who respond well to digitalis is not obligatory, but only an elective method of therapy. It has also been pointed out that marked dilatation of the left atrium, as it occurs in mitral stenosis, represents a contraindication to quinidine treatment because thrombi seem to form more rapidly in overdistended atria. Finally, any evidence of cardiac failure or myocardial damage contraindicates the administration of quinidine, since large doses of the drug are often necessary and quinidine is a cardiac depressant. When quinidine is used, according to many statistics, 2 to 4 per cent of the patients die suddenly from the above mentioned embolisms, ventricular fibrillation and cardiac or respiratory standstill. If anticoagulants are given for 14 days prior to administration of quinidine, the formation of new atrial thrombi is prevented and the danger of systemic embolism is diminished.

Moreover, experience shows that the normal rhythm often does not persist after quinidine succeeds in restoring it. Sooner or later, the fibrillation reappears, particularly in the three conditions with which it is most frequently associated: rheumatic mitral stenosis, hyperthyroidism, and coronary sclerosis. Thus the patient is exposed to the danger by quinidine therapy, and shortly after treatment ends he fibrillates again. Furthermore, such patients feel just as well after successful slowing of the ventricular rate with digitalis as they would if sinus rhythm were present; they fail to note any improvement when the atrial fibrillation is removed and often do not enjoy any benefit. In some cases of mitral stenosis, the restoration of atrial activity will improve compensation. In many

other cases the dilated atria do not contract even when sinus rhythm is present these patients derive no benefit from quinidine therapy In mitral stenosis a long diastole is necessary in order to permit adequate filling of the left ventricle Marked slowing of the heart is often impossible with digitalis as long as sinus rhythm exists but is easily accomplished when atrial fibrillation appears There fore patients with mitral stenosis often feel better when fibrillation replaces sinus rhythm The same holds for patients with attacks of paroxysmal atrial fibrillation which can be controlled by digitalis It is also of interest that subacute bacterial endocarditis occurs only rarely with atrial fibrillation It is therefore clear that one should seriously consider whether or not defibrillation with quinidine would be of advantage for a given patient

It is an old clinical rule not easily explained that pulmonary edema in mitral stenosis and angina on effort in coronary stenosis are rarely encountered after the onset of atrial fibrillation

Thus it happens that even in an active service of a large hospital quinidine is rarely used The presence of indications rather than the absence of contra indications should be the determining factor Quinidine should be given when subtotal thyroidectomy has been performed for hyperthyroidism and when all the symptoms of this condition have vanished with the exception of atrial fibrillation Or it should be used in patients who develop fibrillation during a pneumonia or an infectious disease when the fibrillation persists even though they are otherwise healthy Under these circumstances there is reason to hope that the patient will become entirely well after the fibrillation is abolished and the treatment may be justified

In recent years an attempt has been made to revive quinidine therapy of atrial fibrillation as a routine measure The arguments for this procedure are not convincing and we see no reason to change our attitude

In cases in which defibrillation is to be attempted before quinidine treatment is started the patient should be digitalized until the ventricular rate falls to about 80 per minute As soon as this is accomplished a trial dose of 0 2 Gm of quinidine is given orally to test for sensitivity This must be done because abnormal reactions to quinidine in the form of skin rashes diarrhea and respiratory disturbances are common and unpleasant phenomena Death due to hyper ensitivity has been observed after this one dose (Lone) Kalmansohn and Sampson observed transient ventricular fibrillation following doses of 0 2 Gm of quinidine in two patients In rare cases atrial fibrillation disappears even with this first dose If no untoward symptoms are present on the next day treatment is instituted according to the following plan

Day	*Gm Quinidine Sulfate*
1	3 × 0 20
2	4 × 0 20
3	5 × 0 20
4	6 × 0 20 (or 3 × 0 4 Gm)
5	7 × 0 20
6	8 × 0 20
7	9 × 0 20

Naturally the larger doses are prescribed only if the smaller ones are tolerated Smaller doses (0 2 Gm) are given from 8 a m to 8 p m The larger doses (0 4 Gm) are distributed equally within 24 hours If quinidine causes untoward effects treatment is discontinued In many cases the administration of the smaller doses (0 2 Gm) does not bring the desired result while larger doses such as single doses of 0 6 Gm abolish the fibrillation

On the basis of the estimation of the blood level of quinidine during oral therapy it has been proposed that the drug be administered every 2 hours The results are the same however whether quinidine is given every two hours or three times a day One succeeds in reestablishing sinus rhythm in about 80 per cent of the cases Bedard reversed 89 per cent of his patients with atrial fibrillation to sinus rhythm Four and one half per cent of his patients died suddenly However the doses advised by him were much higher than the average (up to 6 grams of quinidine daily)

If the fibrillation disappears 0 2 Gm is given three times a day for a few more days and then is stopped If fibrillation persists on the eighth day treatment is also discontinued Longer administration of large doses increases the risk beyond reasonable prospect of success If the drug is tolerated well in heavier patients even a dose of 0 5 Gm may be given four times daily on the fifth to seventh day of the treatment The patient must be under close observation and must be confined to bed Due to the atropine like effect of quinidine on the peripheral vagus the ventricular rate may slightly increase when the administration of quinidine is started This is why it is well to avoid the combination of digitalis and quinidine as a routine treatment of atrial fibrillation since quinidine counteracts the effect of digitalis to a certain degree

Thiouracil or radioactive iodine may help in patients with frequent attacks of paroxysmal fibrillation and overfunction of the thyroid

Atrial Flutter

Atrial flutter in man was described in 1910 (Jolly and Ritchie)

Mechanism and Electrocardiogram In this condition the atria contract approximately 300 times per minute that is at a rate in which coordinated movements are still possible Occasionally all stimuli reach the ventricle but usually only a fraction of them (every second third or fourth) is conducted If every fourth beat is conducted regularly to the ventricle the ventricular rate appears normal Very often the number of conducted stimuli varies continually so that diverse arrhythmias appear extrasystoles or atrial fibrillation may be mistakenly diagnosed because of the disturbance of rhythm Atrial flutter a much rarer event than atrial fibrillation appears in the same conditions as the latter and is usually permanent Rarely it appears as a short or longer paroxysm

Figure 103 shows an electrocardiogram of a patient with atrial flutter The patient was a 68 year old man with coronary sclerosis The flutter waves are clearly visible in leads II and III Every fourth atrial wave is conducted to the ventricle (4 1 block) in lead I a 3 1 block occurs once

Diagnosis The clinical diagnosis is possible without recourse to electro cardiography once the existence of this disturbance is suspected and the patient carefully examined

In a minority of cases the rapid regular undulations of the flutter waves are visible if the neck veins are inspected (figure 104)

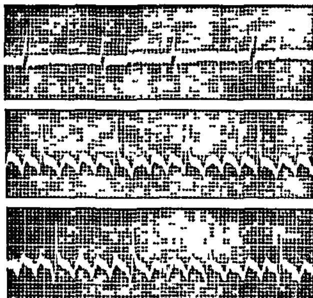


FIG 103 Atrial flutter with 4 1 block

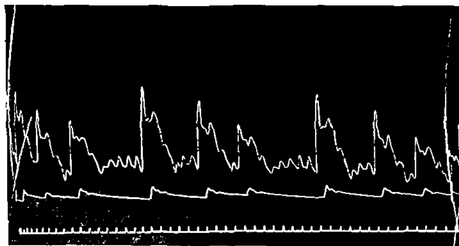


FIG 104 Venous pulse of a patient with atrial flutter and varying A V block the flutter waves (F waves) are clearly visible in the phlebogram

The diagnosis should be suspected in every tachycardia with a ventricular rate of over 100 Ventricular rates of over 300 beats per minute are observed in atrial flutter and full A V conduction While a paroxysmal tachycardia occasionally has this rate it is a usual feature of atrial flutter with full rhythm Frequently with the onset of atrial flutter only every second or third atrial stimulus reaches the ventricle (flutter with 2 1 or 3 1 block) so that the ventricular rate is between 100 and 160 To eliminate a simple acceleration of the heart rate (sinus tachycardia) the patient should be requested to stand to walk a little or if possible to undertake light exercise in the form of climbing stairs or bending In a simple sinus tachycardia a change of posture or slight effort moderately accelerates the rate but this acceleration gradually disappears within a few minutes This is a typical response of the sinus node with normal rate as well as with a sinus tachycardia In atrial flutter however the heart rate remains fixed in all positions even after slight exercise because the abnormal mechanism in the atrium is not influenced by these measures If more strenuous exercise is performed the increased sympathetic tonus improves conduction from atria to ventricles thus a 2 1 block replaces 3 1 block or full conduction appears instead of a 2 1 block The heart rate is increased by exactly 50 or 100 per cent and after a while suddenly returns to its former level The diagnosis is easily confirmed with the aid of the electrocardiogram

Therapy The treatment is not as simple as it is for cases of atrial fibrillation In the latter the rapid and therefore weak atrial stimuli are easily prevented from reaching the ventricle by digitalis which causes a slight impairment of conductivity In atrial flutter however with its less rapid and stronger stimuli the ventricular rate can be reduced only by much larger doses of digitalis and these cannot be administered for any prolonged period of time

There are two methods of procedure quinidine treatment or massive doses of digitalis given in a special way and for a special purpose

Frequently it is possible to abolish atrial flutter with quinidine The method of treatment and the dosage are the same as discussed earlier for atrial fibrillation The danger of peripheral embolism is greatly reduced because atrial contractions in atrial flutter are powerful and thrombi do not occur as often in the appendices as during atrial fibrillation If quinidine therapy fails or is contraindicated because of hypersensitivity or myocardial failure or if myocardial infarction or severe anginal pain exists which makes a quick effect mandatory then digitalis is given The rationale of the digitalis treatment is not to reduce the rate but to transform flutter into fibrillation It has been shown experimentally that an increase of vagal tonus by faradization of the vagus nerve in the neck immediately transforms atrial flutter to fibrillation An attempt is made to accomplish the same result by digitalis via a direct action on the heart muscle and its effect on the vagal tonus For this purpose the administration of digitalis is recommended We have had the best success with digitoxin If five to six tablets of 0 1 mg are given daily fibrillation usually appears on the third or fourth day As soon as this is accomplished it is relatively easy to control the ventricular rate by the

continuous administration of small doses of digitalis. Often sinus rhythm appears spontaneously after the conversion of flutter into fibrillation; if not, it is brought about with quinidine (figure 105).

To be sure, there are cases in which digitalis and quinidine fail to change the existing atrial flutter. If this happens, it is advisable to repeat the same therapy *after an interval of a few months*. In our experience the second or third attempt often yields better results.

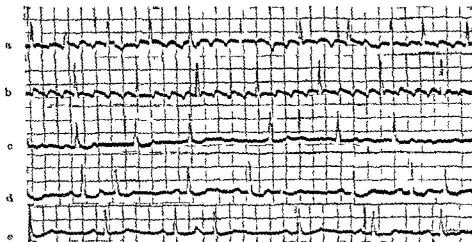


FIG. 105. (a) Atrial flutter with varying A-V block in a 45 year old man; after 0.4 mg of digitoxin was administered daily for two days, a regular 4:1 block appeared. (b) Four days later, after the same daily doses of digitalis had been continued, atrial fibrillation appeared. (c) Then digitalis was stopped. Four days later sinus rhythm with atrial extrasystoles spontaneously appeared. (d) Nine days later the picture is unchanged. (e) The RS-T segments are still deformed by the digitalis effect.

Ventricular flutter and ventricular fibrillation are usually terminal events. They may occur during cardiac catheterization and electric shock therapy. Occasionally patients survive such attacks, some of which have been registered in the electrocardiogram. It is interesting that attacks occurred more often in patients with heart block and during treatment with quinidine. Patients have survived attacks lasting as long as six minutes (Schwartz).

In general, standstill of the circulation lasting longer than 3 to 3.5 *minutes* leads to damage of the cerebral cortex. Therefore, quick action is necessary if ventricular fibrillation appears. The chest must be opened, best between the fourth and fifth left ribs, and the heart must be massaged rhythmically at least 40 times per minute. The intracardiac injection of procaine hydrochloride (5–10 ml. of a 1 per cent solution) or application of electric shocks is then used to stop the fibrillation. This procedure has been successful in many instances (Zoll). The external defibrillator is built on the same principle as the apparatus

in use for direct defibrillation of the exposed heart However the countershocks are much stronger (200 to 700 volts as compared to 120 to 150 volts) The duration of the current is about 0 15 second

CLINICAL ASPECTS OF THE TACHYCARDIAS

The tachycardias can be divided into two main groups sinus tachycardias and paroxysmal tachycardias

Sinus Tachycardia

In sinus tachycardia there is a mere acceleration of the normal (sinus) rhythm This is a physiologic phenomenon that occurs after exertion and during excitement In fever the heart rate usually increases 10 beats per minute for each degree rise of the temperature A sinus tachycardia is also found during and for some time after infectious diseases in hyperthyroidism and in cardiac neuroses and many other conditions

While the cardiac rate is only slightly accelerated in some cases (100—120 beats per minute) a rate of 150—180 is attained in others It is very rare for a sinus tachycardia to exceed a rate of 200

A sinus tachycardia is distinguished from other tachycardias by the fact that (1) the tachycardia develops and disappears gradually and (2) any change of position of the patient and even the slightest exertion increase the rate to some extent Regardless of the existing rate sinus tachycardia in hyperthyroidism becomes faster when the patient rises from the recumbent posture a further increase occurs during walking

Drug therapy of the sinus tachycardia has been quite fruitless Even in a tachycardia with a rate of 180 beats per minute as seen occasionally in hyperthyroidism or a cardiac neurosis no improvement is obtained with digitalis or quinidine Only if a sinus tachycardia is due to cardiac failure can the cardiac rate be reduced by digitalis Employment of prostigmine preparations likewise does not yield satisfactory results The most effective measure is the treatment of the basic disease underlying the tachycardia If hyperthyroidism is treated with iodine or thiouracil the tachycardia disappears within a few weeks In recent years it became evident that in some patients a sinus tachycardia may be abolished with Rauwolfia preparations

If the heart is otherwise healthy little damage is done by a sinus tachycardia even when the rate is high but the harm it causes in the presence of organic changes e g coronary sclerosis is considerable

Paroxysmal Tachycardia

The paroxysmal tachycardias are characterized by sudden onset and an equally abrupt termination If the patient has been aware of the tachycardia its sudden onset and the abrupt cessation will have been noted Often however

no sensation ot palpitation or other abnormality is experienced with very high rates

Three principal forms of paroxysmal tachycardia are distinguished (1) paroxysmal atrial fibrillation and flutter (2) paroxysmal atrial tachycardia and (3) paroxysmal ventricular tachycardia The last two are also known as essential paroxysmal tachycardias A tachycardia originating in the atrio ventricular node (nodal A V tachycardia) is rare but it is often erroneously diagnosed from the electrocardiogram According to Campbell a supraventricular tachycardia is found in 60 per cent of paroxysmal tachycardias paroxysmal atrial fibrillation in 30 per cent atrial flutter in 6 per cent and ventricular tachycardias in 4 per cent

Paroxysmal Atrial Fibrillation and Flutter These disturbances discussed as permanent conditions in the preceding section are often accompanied by a high ventricular rate Since they begin and end suddenly these conditions belong to the paroxysmal tachycardias The complete irregularity permits the diagnosis of atrial fibrillation without an electrocardiogram The diagnosis of atrial flutter was discussed in the preceding section

The significance and treatment of atrial fibrillation and flutter as permanent states was discussed earlier If short attacks of atrial fibrillation or flutter appear several times a week or daily quinidine sulfate should be given prophylactically One tries as in the case of extrasystoles to obtain success with the smallest possible amounts of the drug Only when quinidine cannot be given or is not tolerated is digitalis administered The result is sometimes similar since the attacks occur less frequently or even disappear completely Often however the attacks persist but digitalis reduces the ventricular rate so much that they are harmless Occasionally digitalis transforms paroxysmal fibrillation into permanent fibrillation which is welcome to the patient and the physician since the patient is no longer in constant dread of an attack The permanent fibrillation is usually easily controlled with small maintenance doses of digitalis

If the attacks occur at irregular and long intervals e g once a month prophylactic therapy is hardly necessary Under these circumstances it is advisable to administer quinidine only during the attacks one tablet of 0 20 Gm is given every two hours until the flutter or fibrillation subsides As a rule only two or three doses are necessary until sinus rhythm reappears If there is hyper sensitivity to quinidine one must resort to digitalis

Essential Paroxysmal Atrial and Ventricular Tachycardia Both types of tachycardia consist of a long series of extrasystoles A tachycardia develop because the interval between the extrasystoles is short

The clinical picture of the essential paroxysmal tachycardias has been studied by numerous investigators all over the world for a long time This has been possible because of its prevalence Atrial tachycardias in particular are very common but only a small percentage ever come to the attention of the physician In the majority of cases the attack is of short duration and is un recognized even by the patient Paroxysmal ventricular tachycardias are rarer but by no means as uncommon as some reports seem to indicate

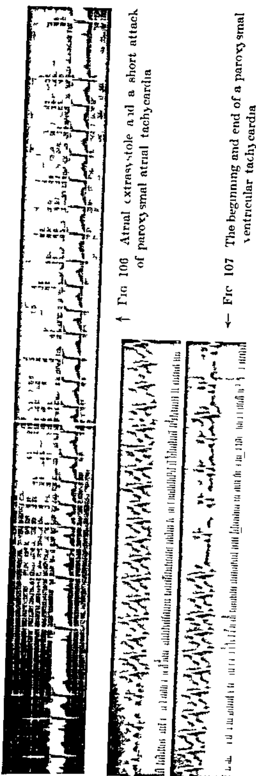


Fig 106 Atrial extrasystole and a short attack of paroxysmal atrial tachycardia

Fig 107 The beginning and end of a paroxysmal ventricular tachycardia

ELECTROCARDIOGRAM Figure 106 shows a short attack of paroxysmal atrial tachycardia observed in a patient with mitral stenosis (lead II) The sudden beginning and the sudden end of the attack are clearly visible The rate of the tachycardia is 150 per minute A single atrial extrasystole appears in the beginning of the tracing

In Figure 107 the beginning and the end of a paroxysmal ventricular tachycardia are shown the rate is about 200 per minute A single ventricular extrasystole appears after the tachycardia ends

In patients with severe myocardial damage the form of the ventricular beats during ventricular paroxysmal tachycardia varies Similar tachycardias appear following the administration of toxic doses of digitalis in patients with myocardial damage

MECHANISM The same two theories as in atrial fibrillation and flutter are usually advanced in order to explain the mechanism of paroxysmal tachycardias The explanation most acceptable to us is that of a rapid formation of stimuli in an abnormal center

ETIOLOGY In the majority of cases attacks of atrial tachycardia occur in perfectly healthy people showing no evidence of organic heart disease In exceptional cases the attacks are related to excessive smoking pregnancy an injection of adrenalin or the administration of strophanthin or digitalis Ventricular tachycardias also may occur without any symptoms of heart disease but often coronary occlusion or coronary sclerosis is present In rare cases reflexes (paroxysmal tachycardia occurring on swallowing) (Sakai and Mori) or exertion (Scherf) are exciting factors In most of the cases

however the attacks occur without any demonstrable cause Patients with abnormal response to digitalis occasionally have a characteristic type of paroxysmal ventricular tachycardia (see later) and this represents an urgent

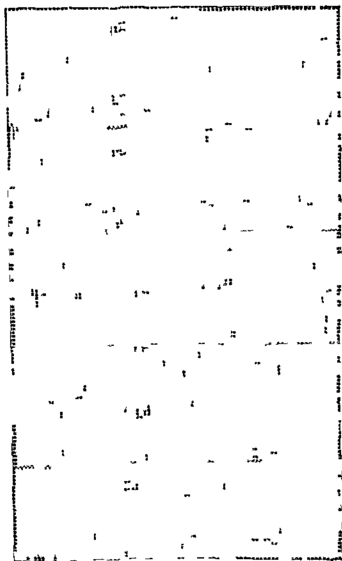


FIG 108 Pre excitation syndrome in a 47 year old man

warning to discontinue the drug Paroxysmal tachycardia has been found at all age and even in infants

About every third patient with the pre excitation syndrome characterized by a very short P R interval and abnormal QRS complexes (figure 108) complains

of attacks of paroxysmal tachycardia Common in these QRS complexes is a slurring or notching of the ascending branch of the R wave The interpretation of this phenomenon as being caused by an accessory A V bundle of conduction (Holzmann and Scherf) is still the most widely accepted one A disturbance of impulse formation in the A V node has been suspected because of misinterpretation of tracings but there is no sound foundation for this assumption (Scherf Blumenfeld and Mueller)

SYMPTOMS Many patients have a fluttering sensation which if accurately described leads to the diagnosis Other patients have palpitation which also should make the examiner suspicious In a large number of cases however only weakness and fainting exist without any unusual sensation in the cardiac area so that the physician who sees the patient after the attack has disappeared has difficulty in reaching the diagnosis Occasionally a patient will describe only a peculiar feeling of anxiety while another has nausea and vomiting (due to hepatic congestion) anginal pain or intense pressure in the cardiac area Meteorism and belching are early complaints In older individuals with atherosclerosis a marked fall of blood pressure with confusion coma or even shock may appear

Of greatest diagnostic importance is the statement that the attacks or sensations start suddenly and end suddenly If the history of the sudden onset and abrupt ending of the attack is elicited the diagnosis is obvious Many patients however particularly those whose hearts are abnormal do not feel the beginning and ending clearly making the positive history alone of value Not rarely the examining physician notes the end of an attack by auscultation but the patient does not feel it has subsided

A peculiar scarcely investigated symptom accompanying various forms of paroxysmal tachycardia is urina spastica the patient reports voiding remarkably large volumes of light colored urine This large amount of urine is passed soon after the onset occasionally during the attack but only rarely after its cessation Since this sometimes unnecessarily alarming phenomenon may occur immediately after the onset of the attack one cannot ascribe it to the disappearance of renal congestion as has been suggested While this phenomenon may be observed in other conditions unrelated to the heart and circulation the finding of urina spastica helps in the differentiation from other forms of tachycardia or palpitation because it is common in paroxysmal tachycardia but very unusual in the sinus tachycardias

Prolonged tachycardias with rapid ventricular action may lead to passive congestion for the same reasons as atrial fibrillation pulmonary edema may even occur Hemoptysis during an attack is not rare and is difficult to explain The temperature is moderately increased presumably due to pulmonary congestion Leukocytosis may be found

The venous pressure is increased the minute volume and occasionally arterial oxygen saturation may fall remarkably The T waves may be abnormal for a few days after a tachycardia (figure 109) (Burak and Scherf)



Fig 109 Paroxysmal atrial tachycardia in a 74 year old man who sought hospitalization for precordial pain Two days after the tachycardia had disappeared the electrocardiogram is markedly altered and shows deep inversion of the T waves in all leads (b) This is not the post tachycardia syndrome described by Burak and Scherf since a normal electrocardiogram was not registered until ten days later The electrocardiogram should have become normal within a few days were the abnormality solely the result of the tachycardia Presumably the patient developed the tachycardia as a consequence of a small myocardial infarction

The size of the heart may decrease during the attack (Scherf and Zdansky) but in a tachycardia lasting over many months with a fast rate, both ventricles may dilate and evidence of relative tricuspid and mitral insufficiency may appear.

The manifestations of paroxysmal atrial or ventricular tachycardia differ in each individual case. The course can never be predicted when the patient is seen in the first attack. Even single attacks may exhibit extreme variations with respect to frequency and duration. An attack may recur repeatedly within twenty-four hours or the patient may have only one attack in years or *in a lifetime*.

DIAGNOSIS. The rapid, regular action of the heart is easily recognized if the rate is over 150, but with slower rates the diagnosis is often missed without the help of the electrocardiogram. The rate may vary in individual cases between 110 and 250 beats per minute. It is always faster than the existing sinus rhythm. The first heart sound is often accentuated, while the second heart sound may be soft, owing to the diminished output and the fall of blood pressure. In other cases embryocardia is present. If murmurs are present during sinus rhythm they disappear during the tachycardia, since the diastole is much too short to permit their appearance and the systolic output is too small to make a systolic murmur audible. With a heart rate of over 180, a correct count of the pulse becomes difficult.

The frequently made diagnosis of cardiac failure with sinus tachycardia causes the patient and his family unnecessary fright. The attitude of the physician in cases of paroxysmal tachycardias is often wrong, and unfounded alarm more often than not exerts a bad influence on the morale of the patient.

In a paroxysmal tachycardia one should determine first whether an atrial or ventricular type exists. Occasionally this is possible by observation of the venous pulse, since in the ventricular form the atria usually do not participate in the tachycardia and independent slow "a" waves may be seen in the jugular veins. The differentiation is made easier by the use of the electrocardiograph. On this occasion a warning may be sounded. Many enthusiastic physicians seek to abolish the attack with carotid pressure and often in atrial tachycardias attain success so quickly that no opportunity is afforded to ascertain what type of attack is present. Since the differentiation between the various types of tachycardia has prognostic significance, one should try — if possible — to take an electrocardiogram before therapeutic measures are instituted. Rarely, even ventricular tachycardias are stopped by carotid pressure.

As pointed out before, the rate of the tachycardia has great importance in the clinical picture. In an atrial tachycardia, the atrial contraction precedes the ventricular and aids the filling of the ventricles. If, however, the atrial tachycardia exceeds a certain "critical rate" (Wenckebach) which usually amounts to 180 beats per minute, diastole is so short that the atria contract while the ventricles are still in systole. Since the atrial systole is superimposed on that of the ventricles, the atria cannot expel their contents into the contracted ventricles and blood moves backward into the venae cavae, producing a particularly marked engorgement of the great veins and of the liver.

The apprisal of the clinical picture is easy when the patient has a long history of attacks and can provide information upon all important details But the problem is more difficult if the patient seeks aid during or after the first attack Then a decision must be deferred until observation permits a reliable evaluation of frequency duration and consequences of the attacks

The same statement is particularly valid in determining the significance of the tachycardia If the patient reports that the attacks have existed for years and examination reveals nothing abnormal one is justified in regarding the tachycardia as a harmless disturbance (cf the statement on extrasystoles) But if patients are seen during or shortly after the first attack they must be observed for a time even when the first examination is negative since the tachycardia may be the first and for a time the only sign of myocardial disease All statements made on this subject during the discussion of extrasystoles are applicable here

DIFFERENTIAL DIAGNOSIS In most cases it is easy to differentiate between paroxysmal tachycardias and a sinus tachycardia In patients who do not feel the sudden start and ending and have only vague symptoms the diagnosis is difficult unless one has the opportunity to observe the patient during an attack

Atrial flutter may be difficult to rule out even with the aid of an electrocardiogram

PROGNOSIS The majority of attacks occur in healthy persons and have an excellent prognosis Even if they recur often the patient is usually able to stop them easily If he is correctly informed by the physician any feeling of apprehension that is present may disappear

The situation is difficult if the attacks respond poorly to treatment or if they last too long or appear too often In rare cases cardiac dilatation and congestive heart failure may be caused simply by the tachycardia and death may occur without any evidence of myocardial or valvular lesion (Scherf and Kisch)

The prognosis of ventricular tachycardias is usually considered worse than that of atrial tachycardias Ventricular tachycardias to be sure may also appear for years in patients who show no evidence of myocardial disease but this is exceptional Usually organic heart disease particularly coronary sclerosis exists occasionally as mentioned above a paroxysmal ventricular tachycardia may be the first sign that a heart lesion is present

Paroxysmal ventricular tachycardia is an ominous complication of myocardial infarction

TREATMENT If the patient is seen during an attack and the diagnosis of an atrial tachycardia is established by means of the electrocardiogram before the administration of drugs an attempt should be made to abolish the attack by one of the numerous vagal reflexes If tried with care and patience they often help and these procedures have the advantage that the patient can be taught to use them whenever the attack recurs

At first carotid pressure described as vagus pressure in older literature is applied It is performed in the following manner the patient must assume the recumbent posture because dizziness and faintness may result from carotid pressure The carotid artery is palpated at the level of the thyroid cartilage anterior to the sternocleidomastoid muscle and is pressed toward the vertebra Cardiac activity is simultaneously observed with the stethoscope The amount of pressure exerted differs in every case In some even the lightest pressure suffices while in others the pressure must be strong If several attempts are unsuccessful it is well to repeat the procedure at a somewhat higher or lower level because the site of the carotid sinus varies and pressure at other points is ineffective In a majority of cases the pressure is effective on the right side but pressure is often successful on the left Obviously pressure should not be exerted on both sides simultaneously Many patients soon learn to apply carotid pressure themselves and can thus suppress attacks readily

An attack of paroxysmal atrial tachycardia existed in the patient whose electrocardiogram is reproduced in figure 110 Carotid pressure on the right side was started at the time indicated by the signal The attack ended abruptly (within a few seconds) and was followed by a complete standstill of the heart for a few seconds because the pressure was exerted too long

If carotid pressure is ineffective other vagus reflexes should be tried Some patients can terminate attacks by holding their breath or by a sudden deep inspiration Others succeed by means of the Valsalva experiment that is maximal activation of the expiratory muscles with a closed glottis The patient should be advised to exert pressure similar to the way during defecation Ocular pressure (bulbar pressure) is often effective particularly in youthful individuals The patient looks downward and closes his eyes then gradually increasing pressure is exerted against the eyeball Occasionally bending forward or bending the knees terminates an attack In rare cases pressure on the abdomen or slight mechanical irritation of the skin in the external auditory canal stops the paroxysm Some patients find that touching the pharynx with the fingers provokes retching and abolishes the attack at once

If all these reflexes are tried — which is easily done within a few minutes — the attacks can be terminated in almost 50 per cent of the cases

The drug which is safest and usually successful within a reasonable time is again quinidine sulfate After a test dose shows that no idiosyncrasy exists a tablet of 0 20 Gm is given every two hours day and night until the attack subsides This is usually the case within a few hours although in some cases treatment has to be continued for a few days This treatment is harmless if the patient shows no untoward sign due to hypersensitivity The patient should rest until the attack subsides

If the patient does not tolerate quinidine he should be given digitalis This drug was more widely used in the prequinidine era and nowadays is neglected by many For this treatment as in atrial flutter digitoxin is recommended Digitalis therapy has been very successful for attacks of paroxysmal tachycardia in child

ren The frequently heard statement that digitalis is useless or contraindicated in the ventricular type of paroxysmal tachycardia is not correct

In the majority of cases the attacks need not be abolished immediately No harm is done while waiting for quinidine or digitalis to become effective therefore this method is preferable to those which are speedier but have some untoward and sometimes unpleasant effects

Often an intravenous injection of quinine dihydrochloride or quinidine sulfate is effective and stops an attack of paroxysmal tachycardia immediately (Singer and Winterberg) Initially only 0 2 Gm should be injected this amount if not effective may be increased if necessary to 0 4 or even 0 5 Gm on the following day or in the next attack provided the first injection was well tolerated As a rule the attacks cease immediately and usually even during the injection The injection must be given very slowly however and it is not always entirely harmless Quinidine is a cardiac depressant even small doses given intravenously may act adversely on a damaged myocardium Since no one can readily determine whether and to what extent the myocardium is damaged in an unknown patient great caution is advised in the use of quinidine or quinine by intravenous injection Slow infusion with control of heart rate and blood pressure is safer Intramus

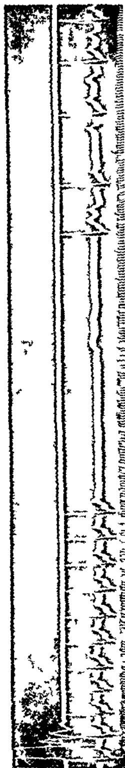


Fig 110 Carotid pressure stops a paroxysmal atrial tachycardia

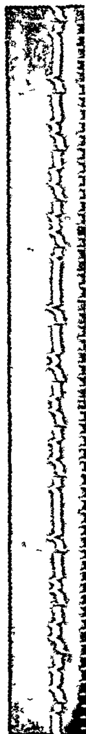


Fig 111 Periodically dropped beats (Wenckebach's period)

cular injections are now possible since preparations are available for this purpose they are devoid of danger in certain cases this route has advantage The injection of a single dose of 0 5 Gm every three or four hours is permissible The same rules obtain for quinidine lactate as for other salts of quinidine

If the patient does not tolerate quinidine or if evidence of heart failure is present digitalis or strophanthin is preferable If quick action is desired the injection of one of the new purified glycosides like Cedilanid (0 4 mg) or digoxin is recommended Still more active is strophanthin which may be given in the dose of 0 25 mg if no digitalis has been administered earlier

Quinidine is superior to digitalis when attacks recur often and prophylactic measures are indicated In this case one proceeds exactly as in the treatment of extrasystoles or paroxysmal fibrillation and seeks to determine the smallest amount effective in preventing the tachycardia

Among the numerous other drugs recommended for the treatment of paroxysmal tachycardia choline or the much more effective derivative acetyl beta methylcholine was found helpful It abolishes the tachycardia in about 85 per cent of the cases The dosage depends upon the weight and age of the patient usually 30 to 40 mg subcutaneously suffice One must have a syringe with atropine ready in case untoward symptoms appear While these are rarely dangerous they are often unpleasant Adenosine triphosphate has been used with success (Komor and Caras) Vagus stimulation by physostigmine often used in the past has been abandoned but prostigmine (0 5—1 0 mg subcutaneously) has less side effects than mecholyl All these compounds are rarely used today

Emetic drugs have also been recommended but the simple suggestion to the patient to induce retching by inserting two fingers very deep into the throat has the same effect without other unpleasant reactions

Pressor amines such as neosynephrine Vasoxyl and Isuprel abolish attacks of supraventricular tachycardia but they may elicit dangerous ventricular ones The intravenous injection of 0 5 to 1 mg of neosynephrine has been advocated in paroxysmal atrial tachycardias It has been suggested that this dosage be repeated when the blood pressure is normal after 30 seconds however ventricular extrasystoles are common when pressor amines are injected intravenously and they bring danger

It is astonishing what heroic measures and even dangerous drugs have been recommended for this harmless condition which so rarely endangers the life of the patient and for which more conservative methods of treatment usually suffice Apomorphine for instance and even adrenalin were recommended the latter will often abolish the tachycardia but in a certain percentage of cases will cause ventricular tachycardia or even fibrillation

Among the recently recommended drugs magnesium sulfate is often useful Fifteen to twenty ml of a 20 per cent solution are given intravenously No untoward symptoms were seen by the authors in a series of about 60 cases and none have been reported by others injecting this drug in patients with paroxysmal tachycardia Since stronger solutions of magnesium sulfate paralyze the heart

muscle the injection must be given slowly It is contraindicated in patients with a damaged or weak myocardium

In a paroxysmal tachycardia refractory to quinidine in safe dosage and not responding to oral administration of Pronestyl an intravenous injection of Pronestyl may be attempted It should be done very slowly with continuous control of the blood pressure Side effects often appear — as with quinidine — in elderly patients and in patients with a damaged myocardium The necessary dose varies Not more than 100 mg per minute should be injected (Kerry et al) usually 300—1000 mg are needed

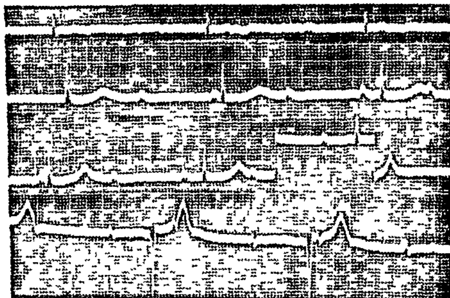


Fig 112 Complete dissociation between atria and ventricles (complete heart block)

Bellet et al noted good results with an intramuscular injection of Pronestyl gluconate or hydrochloride in the dose of 0 5—1 5 gram In this way the severe hypotension which may follow if these drugs are given intravenously is avoided

Of great interest is the employment of potassium preparations in the treatment of paroxysmal tachycardia and extrasystoles The effect of potassium on stimulus formation of the heart has been known since the classical studies of the action of electrolytes on cardiac activity by Loeb Ringer and others It has been recognized that potassium inhibits stimulus formation and in this regard is antagonistic to sodium and calcium The administration of potassium salts by mouth increases the blood level and causes the extrasystoles and paroxysmal tachycardias to disappear (Sampson Anderson) However the dosage is difficult to determine since the effective doses vary in different persons Even in patients with normal renal function dangerous arrhythmias have been observed after oral administration of potassium



Fig 113 Stethogram of a patient with complete A V block the loud systolic aortic murmur was transmitted to the apex The stethogram was obtained from the apical area and clearly shows the *marked accentuation of the first heart sound of the third beat in figure 113* when atrial systole precedes the ventricular one by about 5 hundredths of a second

Two grams are given at the beginning and 1 to 2 grams are repeated every two hours until the attack subsides Potassium iodide is usually recommended Other salts like potassium chloride or acetate are also effective The combination with quinidine has been advised (Stempien and Katz) Following the ingestion of a potassium salt the blood level begins to rise in about 30 minutes and reaches its maximum in two to three hours A blood level of 33 3 mg per cent of potassium was obtained in this way Sweating and nausea may appear

A rapid intravenous injection of a potassium salt leads immediately to ventricular fibrillation

Conduction Disturbances

Various arrhythmias sometimes of complex structure may be caused by sinoatrial or more frequently by an atrioventricular block Only a few remarks concerning these disturbances can be included in this book For a complete discussion the reader is referred to our textbook on electrocardiography

The simplest and most common conduction disturbance is the prolongation of the P R interval (figures 22 and 94) This causes no disturbance of rhythm and may be suspected only by the presence of a presystolic gallop rhythm Next in frequency is a periodic dropped beat where as in figure 111 the atrial stimuli are conducted progressively more slowly to the ventricle until one atrial impulse is blocked The conduction system recovers the conduction returns to normal or at least is improved for one beat and then the progressive fatigue reappears This condition first described by Wenckebach is now called Wenckebach s period

In the two conduction disturbances described above and in higher degree of partial as well as in complete atrioventricular block (figures 70 and 112) one must at first rule out digitalis therapy as the etiologic agent Digitalis in large quantities is a typical cause of these

conduction disturbances if given when the heart is already damaged even relatively small doses may produce various types of conduction disturbances or even complete heart block If treatment with digitalis did not precede the appearance of heart block then an organic change in the conduction system must be assumed to exist As pointed out in the preceding chapters there are three lesions in which heart block appears very often One is rheumatic fever which seems to possess a peculiar and unexplained affinity for the atrioventricular conduction system The second condition is coronary sclerosis and the third diphtheria It has been mentioned that particularly in an occlusion of the posterior descending coronary artery (right coronary artery) different types of heart block appear Partial and more often complete heart block are also found in congenital ventricular septal defects

Complete A V block can be recognized by auscultation One of the most characteristic signs is the presence of the cannon sounds over the apical area In the presence of a regular heart action one hears periodically a very accentuated often tympanitic first heart sound This does not occur when atrial and ventricular contraction coincide it is present as shown in figure 113 when the atrial contraction precedes the ventricular one by about 5 hundredths of a second For the explanation of this and the discussion of other signs of A V block we refer to our companion book on Clinical Electrocardiography

No specific treatment is necessary in heart block the management of the patient is that of the underlying disease There is only one serious accident in the course of the development of a complete block namely Stokes Adams attacks These were discussed in another chapter where emphasis was directed to the fact that the appearance of this syndrome requires not only a conduction disturbance but also damage to the automaticity of the deeper ventricular centers

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Chapter 30

Peripheral Vascular Diseases

Introduction

Our knowledge of peripheral vascular disease has increased tremendously in the past 40 years For a long time these conditions were investigated and discussed mainly by neurologists (Charcot Erb Weir Mitchell) and were ascribed almost exclusively to a nervous vasospasm In his paper describing erythromelalgia Mitchell called the lesion a rare vasomotor neurosis while Cassirer entitled one of the early monographs on peripheral vascular diseases Vasomotor trophic Neuroses Since then we have learned to differentiate many pathologic entities which can be distinguished clinically by a detailed history and careful examination New methods of examination permit the differentiation between vascular disorders due to organic obstruction and those caused by vasospasm

Recent therapeutic innovations may save limbs from amputation but even at present early lesions are still too often attributed to fallen arches or rheumatism although these errors are less frequent than a few years ago

The peripheral vascular lesions are best classified as organic or functional disturbances The former group can be subdivided into inflammatory processes such as thromboangiitis obliterans or lesions due to tuberculosis typhus syphilis and so forth while another group involves degenerative lesions such as arteriosclerosis Periarteritis nodosa seems to be an allergic phenomenon The functional group includes disturbances such as erythromelalgia acrocyanosis and certain types of the Raynaud syndrome

The lesions resulting from arterial embolism or arterial as well as venous thrombosis form a separate group Only the more common and the more important lesions will be discussed in this book

Symptoms

The frequent combination of inflammatory or degenerative vascular alterations with functional spastic disorders causes diversified clinical pictures The localization the time of appearance of the lesions and many others factors vary according to the nature of the disturbance most complaints of the patients however are the same even when the etiology differs Therefore we shall discuss some of the symptoms at the outset and subsequently add the details characteristic of the different lesions in corresponding sections

Pain This is the most common symptom Often it appears in the calf hip or in the foot during walking occasionally it is also felt at rest and it may come at night particularly if the leg is held in certain positions Sometimes it is constant All transitions between mild gnawing and most excruciating pain are encountered

If pain in the calf appears on walking the patient may be forced to stand still This is known as intermittent claudication The history indicates clearly that the pain occurs after walking a certain distance and disappears a few minutes after stopping Similar to the anginal pain on effort walking for a long time at home even climbing of stairs need not cause the pain This distance may remain constant for a long time and deterioration of the patient s condition as well as any improvement are clearly reflected by shortening or lengthening respectively of this distance

It has been clearly demonstrated that an accumulation of a stable physico chemical stimulus in the tissue spaces (Factor P) the consequence of the lack of oxygen in the muscle fibers is responsible for the pain Possibly the lactate ion is the agent involved in the chemical stimulus (Elliott and Evans)

Intermittent claudication may appear in the absence of vascular disease e g in mitral stenosis or in coarctation of the aorta — whenever that is the difference between the supply of blood to the leg muscles and the needs is disproportionate

In general pain at rest is more unfavorable from a prognostic standpoint than pain on movement The absence of pain during rest does not however indicate an adequate blood supply since pain may be absent in embolism with complete occlusion of the femoral artery and resultant gangrene Pain at rest may indicate impending trophic disturbances and particularly in thromboangiitis obliterans it may be due to an ischemic neuritis

One must differentiate between rest pain in peripheral vascular disease and night cramps which appear in healthy people particularly when toward morning the legs are stretched The mechanism of this pain during which the calf muscles become as hard as a board is unknown Several therapeutic measures have been recommended such as vitamin sodium chloride Benadryl and calcium According to our experience 0 2 Gm of quinidine sulfate taken before retiring helps more than other drugs

Patients with so called restless legs (Ekbom) feel sensations of cold weakness paraesthesias and sometimes pain in the legs and thighs which disappear when they stand or walk The cause is unknown

Fatigue Weakness and fatigue in the limbs are also common and often are the early signs of a disturbed circulation

Paraesthesias and Coldness Often patients complain of numbness tingling pins and needles and other paraesthesias A burning sensation may be present Rarely an unusual coldness is felt in certain parts of the extremities but this finding is by no means characteristic of peripheral vascular disease

In rare cases patients seek advice because parts of the limbs show abnormal discoloration

METHODS OF EXAMINATION AND INTERPRETATION OF FINDINGS

Inspection Inspection of the affected extremities often reveals an abnormal color With widening of the venules in the subpapillary plexus the blood flows slowly and more oxygen is delivered to the tissues so that cyanosis appears Obstruction of an artery in the absence of collateral circulation causes abnormal pallor Increased redness is present if inflammation or other factors cause dilatation of arterioles capillaries and veins A dark violet color is seen in complete or almost complete arterial obstruction with imminent gangrene

These discolorations may be found over the entire extremity in the toes or fingers or in small patches of the shins Differences in the color of the two limbs exposed to the same temperatures are of great importance because symmetrical cyanosis appears under normal conditions when the peripheral vessels dilate abnormally due to a variation in vascular tone and is not necessarily pathologic

The skin may be edematous thickened or thin and atrophic Its texture is often altered The hairs may disappear locally Small ulcers may be present Even muscles may atrophy One should look carefully between the toes for evidence of epidermophytosis

Examination of the nails often reveals trophic disturbances The normal longitudinal ridges are increased and transverse ridges appear The nails may become discolored and may loosen from their bed they may grow slowly or stop growing altogether

Palpation Temperature of the skin is estimated with the palm or the ulnar surface of the examiner s hand He should test the extremities after they have been exposed for 10 to 15 minutes to room temperature The finding of an equally cool skin over both extremities is without great importance because this may be normal but even small differences between the two sides tested after sufficient exposure to room temperature have great significance The level at which a difference of temperature begins should be ascertained A slight difference of temperature is often discovered over the knee at a time when no other place shows significant change A temperature difference of as little as 0 5 C can be detected by palpation Sometimes the affected leg is warmer than the healthy one or the more affected leg is warmer than the less involved one The local temperature is lower when there is perspiration sometimes the more affected limb sweats less profusely than the healthy one

If blanching of a circumscribed area e g the ball of the toe is caused by pressure of the finger normally the ischemic area rapidly becomes perfused again when the pressure ceases The slow return of the color is occasioned by diminished flow of blood while a more rapid flow or increased pressure in the vessels particularly in the venules may cause an acceleration It is true that a prompt return to the previous color may be seen even if circulation in a deeply cyanotic leg i

arrested completely slight differences on the two sides however are important for they are early indications of an abnormality in the circulation This test gives the best results when performed with the involved extremities slightly elevated

Examination of the pulsation in the arteries of all four extremities is the next step In the arms one examines the subclavian and axillary arteries the brachial radial and ulnar arteries at the well known areas

In the lower extremities the femoral artery is palpated at Poupart s ligament midway between the symphysis and the anterior superior spine of the os ileum and followed to the triangle of Scarpa The popliteal pulsations are examined best with the patient prone and the leg slightly flexed at the knee In obese patients the popliteal pulsation is recognized only with difficulty The dorsalis pedis artery is palpated on the dorsum of the foot between the proximal ends of the first and second metatarsal bones and lateral to the tendon of the extensor hallucis longus muscle A search for the pulsation of the posterior tibial artery is made behind and a short distance from the internal malleolus

Occasionally pulsation of the two last named arteries is not found on one or both sides in normal people The location of the vessel may vary The dorsalis pedis artery runs a different course over the dorsum of the foot in about 8 per cent of cases Statistics indicate that the artery is absent in about 4 per cent of people bilaterally and in 12 per cent on one side only Variations in the course of the radial artery are even more common

In some patients vascular spasm makes an arterial pulse imperceptible Therefore before it is declared absent it has been recommended that the arteries be palpated shortly after the patient has taken a tablet of nitroglycerin Sometimes the vessels feel sclerotic and do not show pulsations because of deposits of calcium in their walls They are however patent In order to avoid confusing the patient s pulse with the pulse in his own fingers the examiner should palpate the patient s radial pulse at the same time

Although the finding of slight differences on the two sides is important for the diagnosis the occurrence of unilateral variations is so common that no diagnosis should be based on the absence of a pulsating dorsalis pedis artery or an absence of pulsation of the posterior tibial artery on one side alone

Some patients have no pulsation for years in an artery owing to vascular disease but they have no complaints In such instances the arterial obstruction is fully compensated by collateral circulation On the other hand severe trophic disturbances and even gangrene of the toes may appear with the pulse palpable in all major arteries in a limb This happens when the process involves arteries lying distant from those palpated

The following is a useful test for discovering obstruction of the ulnar or radial arteries The patient is asked to close his hands as tightly as possible in order to squeeze the blood out of the palm The ulnar and radial artery are then compressed and the patient opens his fist The pressure on these arteries is released one after the other and the return of color is noted An occlusion of the ulnar

artery for instance is diagnosed if the color does not return with the release of compression on this artery but quickly returns when the pressure on the radial artery is released (Allen) At the same time as the pulsations are felt an attempt is made to determine the condition of the arterial walls

If a distinct pulsation is elicited from the dorsalis pedis artery it should be determined whether or not the pulsation disappears when the leg is elevated from the horizontal toward the vertical position Normally the pulsation should persist at least until an angle of 45 degrees is reached Often it is found in all positions If elevation of the leg to less than 45 degrees causes the pulsation to vanish the existence of organic arterial disease in the lower extremity may be suspected

Blood Pressure The results of palpation can be supplemented in some cases by the measurement of the blood pressure If the blood pressure cuff is placed on the thigh and the pulsations are palpated in the dorsalis pedis artery normally the blood pressure in the lower extremities at least equals the arm reading and usually exceeds it In pathologic processes involving the large arteries of the lower extremities the blood pressure may be much lower on the affected side

Color Changes with Change of Position Of great value is the observation of color changes of the skin after change of position of the leg (Buerger) The patient lies on his back and exposes his legs to the room temperature for about 10 minutes Then he lifts both legs to an angle of 60—90 degrees and maintains this position for about 2 minutes Simultaneously the patient is requested to perform plantar and dorsal flexion of the foot and toes The legs of the weak patient should be supported by the examiner during the period of elevation Under pathologic conditions marked pallor appears over the entire foot or parts of it and here again differences on the two sides have great significance The pallor is noted more often on the plantar surfaces than on the dorsum of the foot Subjective complaints are usually absent although pain occasionally appears If the patient remains in this position for a longer time small red patches may appear amidst areas displaying cadaveric pallor The patient then assumes a sitting position with the legs hanging down Under normal conditions within five to ten seconds the feet become flushed With obstruction of the arterial blood flow the flush appears irregularly and tardily Due to this delay the color is intensified and may be a very bright pink

If such pink areas are rendered ischemic by means of momentary finger pressure subsequently they redden with extraordinary rapidity in comparison to the healthy side The presence of an enormous acceleration of the blood stream may be deduced from the light red color and the rapid disappearance of any anemia produced by pressure

As a rule these changes indicate structural alterations of the arteries but they are also observed in conditions with an abnormal vasomotor tonus

Filling Time of Veins If the legs are elevated the veins on the dorsum of the foot collapse If the patient sits with the legs hanging down the veins refill as greater arterial pressure and arterial blood flow returns The return of venous

filling under normal conditions requires less than 10 seconds A prolongation of the venous filling time indicates obstruction to the arterial blood flow

Reactive Hyperemia This examination may be supplemented by the reactive hyperemia test After being kept in a warm bath for ten minutes the extremities are dried and maximally elevated until some blanching occurs The remaining color is removed by massage While the extremity is still elevated a cuff high on the upper arm or thigh is quickly inflated above the systolic pressure The compression should be maintained for about five minutes — this time is shortened only in patients in whom arterial thrombosis threatens During the period of interruption of blood flow the extremity is kept in the warm bath maintained at a temperature of 35—40 C in order to avoid vascular spasm At the end of the five minute period the extremity is dried and the cuff is deflated The time elapsing until the flush begins to appear is determined and one observes whether it is symmetrical in all parts of the extremity The flush — the reactive hyperemia — normally appears in about five seconds Under abnormal conditions it is delayed even to more than one minute in small or large areas of the leg and appears in some areas earlier than in others The color changes are similar to those seen in the test with elevation of the legs The vasodilatation is due to slowly diffusible substances formed during the arrest of the circulation

With marked diminution of cutaneous blood supply disturbances of sensation are commonly found

The investigations just mentioned can be performed by every physician without the aid of special instruments and often suffice to indicate the presence and extent of a disturbance in the arterial blood supply to a limb These results can be supplemented by a series of other examinations

Oscillometry With this method the pulsations of the arteries lying under the cuff are transferred to an instrument and produce according to the pressure in the cuff corresponding movements of a pointer These movements do not occur when the underlying arteries fail to pulsate This may be due to an occlusion higher up or at the level of the test Absence of pulsation may also be the result of great rigidity of the arterial walls Therefore an artery may not pulsate although its lumen is patent The collateral circulation is not shown by this test The blood supply to an extremity may be adequate in the absence of oscillatory pulsations in fact oscillations in the legs may be missed in some patients who have remarkably few complaints and only a few other signs of abnormal blood supply The condition of the patient may undergo marked improvement without any increase in the amplitude of the oscillations

Conclusions drawn from the absolute size of the oscillations are of no value because they vary in the same areas in different individuals Even in healthy subjects oscillations on both sides may differ Different results are obtained at different times of the same day even when the same area is examined The size of the oscillations depends upon many factors other than the state of the wall of the examined vessel owing to the existence of many variables Even differences on the two sides can be evaluated only if they are marked

In view of these difficulties it has been proposed that in cases of peripheral vascular disease in the lower extremities the excursions with the cuff just above the ankle be compared to those obtained when the cuff is just above the wrist If the reading of the lower part of the leg is used as a numerator the ratio under normal conditions is at least 1 0 that is the oscillations in the lower part of the leg are at least equal to those in the lower forearm If the ratio is lower than 1 0 a peripheral vascular disease involving the lower extremity is present

If conclusions are drawn with caution oscillometry is valuable Often it helps to demonstrate the site of an embolic or thrombotic occlusion and it reveals pulsations of large arteries where pulsations of peripheral arteries are missing

Measurement of Temperature Of value in estimating the progress of peripheral vascular disease and indispensable for the estimation of vascular spasm is the measurement of the temperature of the skin with the aid of a skin thermometer or a thermocouple

The limbs to be examined are exposed to room temperature of 20° C for about 20 minutes A higher temperature should be avoided because even in the presence of peripheral vascular disease the skin readily reaches the temperature of the room Under normal conditions in a cool room (16—18° C) the fingertips are rarely under 20° C while in a warm room (20° C) they are around 32° C Here again differences on the two sides are very important The normal skin temperature varies Usually it is lower in nervous patients because of perspiration

In a large series of observations it was found that normally the temperature of the skin of the arms is slightly above 32° C and 1 to 2 degrees less in the lower extremities Variations from these figures are encountered

The differences on the two sides have greater importance than absolute values since variations are great even in the healthy Differences found in the normal leg in different persons may amount to 8° Still more valuable is information about changes of temperature after maximal vasodilatation and after abolition of any vasospasm present

Vasodilatation Vasospasm disappears in deep general anesthesia following paravertebral block peripheral nerve block after the consumption of large quantities of alcohol the administration of nitrites and in the lower extremities following spinal anesthesia The safest and best way to relieve vasospasm is to bathe the two extremities not under examination in water of about 45 C This simple method usually suffices in patients with unusually high vasomotor tonus however at times no effect is seen Under normal conditions the skin temperature over the toes after vasodilatation will approach the temperature of the body and it is always higher than 31° C The vasodilatation that results from warming distant parts of the body is not caused by a reflex mechanism it is due mainly to warming the vasomotor centers by the blood flowing to them from the bathed parts of the body (Pickering) This simple test is also preferable to measurement of the skin temperature before and after induced fever by the injection of typhoid vaccine or in a sweating cabinet Another method widely used is the

peripheral nerve block e g blocking of the posterior tibial nerve by an injection of novocaine behind the internal malleolus for the diagnosis of lesions of the toes

With these methods the degree of vasoconstriction is estimated furthermore the presence of an early organic occlusion is detected if the temperature does not rise sufficiently Finally the capacity of vasodilatation is estimated in order to ascertain the advisability of operative intervention on the sympathetic nervous system If the temperature does not go higher than 28 C sympathectomy is not recommended

Histamine Test On the basis of investigations by Lewis histamine injected intradermally was recommended as a test for the vascularization of the skin (Starr) The skin is cleaned and a few drops of 1 1000 solution of histamine acid phosphate are applied to the spot to be tested If the skin is pricked with a needle through the histamine solution without causing bleeding a wheal surrounded by a red flare appears within five minutes

Under pathologic conditions with impairment of blood supply the wheal is reduced in size delayed in appearance or may be absent If the wheal is absent the blood flow is reduced to a minimum or arrested and gangrene is imminent A moderate decrease of blood flow has no influence on the outcome of the test If the test yields an abnormal result the circulation is definitely affected The test has proved particularly useful for estimating the viability of tissue

The intradermal injection of 0 2 ml of histamine solution has the same effect

Roentgenography An x ray film of the leg may confirm the diagnosis of an arteriosclerotic vascular disease through the discovery of lime salt deposits in the vessel wall But medial sclerosis is often present for many years in the leg arteries without any signs of peripheral vascular disease being evident Positive x ray findings are observed even in 40 year old patients without complaints and without evidence of peripheral vascular disease Calcification of lower extremity vessels is found in 65 per cent of men and 28 per cent of woman over 50 years of age Mural calcium deposits in the arteries of the legs do not indicate narrowing of the arterial lumen Therefore the discovery of such deposits has dubious value in diagnosis and in evaluating the degree of the lesion Different x ray patterns of the calcium deposits are observed in medial sclerosis as compared to atherosclerosis (Lindbom)

Angiography Visualization of the arterial vascular tree after intra arterial injection of some radiopaque substance can furnish worthwhile information if carried out by experienced physicians The same holds for venography Complications resulting from the injection may occur even thrombosis leading to gangrene complications may be caused by sensitivity to iodine The test should be performed only under exceptional circumstances such as preoperatively in the Leriche syndrome

Other Tests Examination of the skin capillaries under the microscope does not supply much information that cannot be secured by other methods The blood supply to the skin is also estimated by intravenous injection of fluorescein and the study of the skin with the aid of a special long wave ultraviolet light in

a dark room The use of infrared photography is limited largely to the discovery of subcutaneous veins not visible on mere inspection

THROMBOANGIITIS OBLITERANS

Among the occlusive peripheral vascular diseases thromboangiitis obliterans shares first place with peripheral atherosclerosis These conditions together comprise almost 95 per cent of peripheral vascular lesions

The involvement of arteries and veins together was recognized as characteristic of the disease as early as 1878 (Winiwarter) The condition was described in great detail and was named by Buerger

Incidence

The disease usually occurs in young males The incidence in females is estimated to run about 1 to 2 per cent of that of males Until a few years ago only 22 instances in women had been reported (Collens and Wilensky) It seems that this disease is becoming more uncommon Allen Barker and Hines found an incidence of 1 5000 in Rochester Minnesota residents

Thromboangiitis obliterans occurs at practically all ages It has been observed in patients of 15 years one patient was 79 years old A majority of those affected are between 30 and 50 The disease has been reported in brothers

A peculiar susceptibility of the Jewish race was reported It is certain that the disease has been observed in most races and is common in Japan The full blooded Negro has been said to be free from the disease

Etiology

The cause of the disorder is unknown Infection was considered as the most likely etiologic factor since inflammation is always present (Buerger) This conception received support from reports of the successful transmission of the condition by transplantation of a resected involved superficial vessel A variety of microorganisms have been found in the lesion but these reports remain unconfirmed

Injuries of the tissues as a result of exposure to cold have been considered an etiologic factor Since the disease is usually seen in heavy cigarette smokers tobacco with its numerous active constituents as well as cigarette paper was supposed to be responsible While smoking definitely aggravates the condition no proof is available to show that it produces the disease thromboangiitis obliterans also occurs rarely in non smokers

Allergy to tobacco to proteins derived from fungus infections or to ergotism from rye were also blamed Typhus infection has also been considered responsible

The relative immunity of women suggested the presence of estrogenic hormone as a protective factor and treatment with estrogens was recommended on this basis (Snapper)

Pathology

For the most part the disease involves the vessels of the lower extremity Involvement of the arm vessels is less common However the process has been found in the coronary arteries the cerebral vessels gastric and mesenteric arteries Many patients with thromboangiitis obliterans die from coronary thrombosis but usually coronary atherosclerosis is found at post mortem

The pathologic findings are characteristic Segments of arteries and veins are enmeshed in fibrotic tissue The arteries are occluded by fibrous tissue which because of recanalization presents a cribriform appearance Thrombi develop in both arteries and veins The nerves are also included in the fibrotic mass

The process often begins as a migratory phlebitis If an artery becomes involved lymphocytes and leukocytes infiltrate all three layers of its wall Intimal proliferation appears early and secondary thrombosis may follow The artery however is often occluded by intimal proliferation alone In the veins only thrombosis is found Giant cells appear and recanalization progresses slowly The nerves show an ischemic neuritis Wallerian degeneration and evidence of lymphocytic infiltration (Barker) occur The nutrient vessels of the nerves are thrombosed

The disproportion between the extensive occlusion of the large main arteries and the trifling nutritional disturbances is astonishing Even occlusion of the femoral artery is not regularly followed by gangrene (Jaeger)

Symptoms and Signs

Migratory Phlebitis Some of the earliest symptoms are provoked by the migratory phlebitis The incidence of this phenomenon is estimated at 70 per cent although some find it in only 10 per cent of their cases (Telford and Stopford) We noted it in about 20 per cent of our material Inquiry should be made about red painful areas on the dorsum of the foot particularly in the vicinity of the ankles or the lower leg as well as on the lower arm Usually nonvaricose cutaneous veins are affected Pain redness and tenderness are found Slight malaise and a little rise of temperature are present Often a portion of the vein about 2 to 4 inches in length is involved In some cases however the inflamed area is smaller and confusion with erythema nodosum or erythema induratum of Bazin occurs The period of acute inflammation lasts about 10 to 12 days and is followed by brown pigmentation One gains the definite impression that the adventitia and the neighboring tissue participate in the inflammatory process

Whenever a migratory phlebitis appears it should arouse the suspicion that a thromboangiitis exists or is developing thereby requiring a careful examination of the peripheral arterial circulation

Pain One of the earliest symptoms is pain In general it is more severe than the pain in atherosclerotic peripheral vascular disease but all degrees between mild pain and excruciating agony are encountered Often the pain appears for the first time after exposure to cold

Intermittent claudication is found in 98 per cent of cases (Goldsmith and Brown) It is felt not only in the calf but also in the foot This pain is not knife like rather it resembles a cramp As in angina pectoris which has the same mechanism the pain often occurs after progressively shorter intervals and lasts longer after cessation of activity Rest pain may be due to impending trophic disturbances such as ulcers or gangrene The rest pain is caused by the arteritis and phlebitis as well as the concomitant inflammation in the surrounding tissue It is also a result of the involvement of the nerves so called ischemic neuritis The latter condition in particular causes pain of unusual intensity The sharp shooting lancinating pain is felt in the whole extremity The patient may consume large quantities of narcotics without much benefit Lack of sleep and lack of food cause rapid loss of weight There is no satisfactory treatment for this type of pain *although even chordotomy has been performed for its relief* It is a difficult task to bring the patient through this period occasionally possible only by the repeated assurance that the pain is of temporary character It may last however for many months and has even driven patients to suicide

Occasionally the pain due to tissue dystrophy is partly relieved when the *leg is kept down Patients may sit day and night on the edge of the bed holding* the involved foot (which is crossed over the healthy leg) in their hands massaging it and letting it hang down from time to time This ischemic pain is often aggravated by coexistent vascular spasm initiated by the involvement of the adventitia and causing irritation of autonomic nerves the spasm is accompanied by blanching *If the tests described above show that spasm is responsible to an appreciable degree* its abolition brings quick relief

Other Symptoms and Signs Heaviness and weakness in the legs as well as paraesthesias are early symptoms

Edema is caused by increased venous pressure and damage to the capillary endothelium In some cases ulcers and gangrene appear in or *between* the toes early in the process

The signs of arterial obstruction discussed on the preceding pages are observed on examination At the beginning and sometimes persistently, the process is unilateral Femoral pulses may be absent in patients who come with trifling complaints If the interosseal and digital arteries alone are *involved* the peripheral pulses obtained at the usual places may be normal Fungus infections cause early complications and should be searched for assiduously Occasionally the arm arteries are also affected — cases are known in which amputation of all four extremities was necessary However if the upper extremities are affected it is rarely necessary to amputate more *than a finger*

The appearance of symmetrical vascular changes in the arms may simulate a Raynaud like picture Among 389 cases of thromboangiitis obliterans the legs alone were involved in 74 per cent both arms and legs in 24 per cent and the arms alone in only 2 per cent (Brown)

Fever may be present The sedimentation rate is usually *increased*

Course

The course of the disease varies. Progress may be very slow or stormy. Some cases manifest no more symptoms than those of recurrent thrombophlebitis and the arterial involvement is discovered only by careful examination. These patients have no other complaints during a long period of observation. In some who complain of intermittent claudication, years elapse between exacerbations. With canalization and development of sufficient collateral circulation, symptoms may even gradually disappear. In other observations, the advance may be rapid and the first episode may lead to gangrene. Sometimes the process is fulminating from the beginning, leading within a few days to the purple discoloration of developing gangrene.

The course is unpredictable, but with modern treatment the necessity for amputation is much rarer than formerly. This is partly due to the fact that amputation is performed much later than previously. We have learned that despite very advanced nutritional changes, remarkable improvement may appear suddenly even when amputation seems inevitable.

Differential Diagnosis

This may offer great difficulties, particularly in men over 50, when the condition must be distinguished from atherosclerosis. The presence of a migratory phlebitis is of diagnostic importance. The discovery of calcified vessels in x-ray pictures of the legs has small value in patients over 50 because it is so common in the average individual of this age without peripheral vascular disease. It has been claimed that arteriography shows a different pattern of anastomoses in thromboangiitis obliterans as compared with atherosclerosis (Edwards).

Confusion of thromboangiitis obliterans with ingrown toenails occurs and may lead to unnecessary and detrimental operations.

The differentiation of the condition from Raynaud's disease or peripheral embolism is usually easy.

Treatment

Treatment cannot be directed against the etiologic factor of thromboangiitis obliterans. As soon as the disease is recognized by the discovery of a disturbed peripheral blood supply, active therapeutic measures should be undertaken to prevent further damage to the peripheral circulation and to improve collateral circulation. It seems that in most cases, careful observation of the measures discussed below can prevent gangrene and amputation. Even if new exacerbations cannot be prevented with certainty, much can be accomplished.

Hygienic Measures. Since the arterial blood supply to the tissues is diminished, the first efforts should be directed against any increased demands. If these demands cannot be fulfilled, nutritional changes are the consequence. Rest is therefore necessary. Local heat, which was widely used in the past, is strictly forbidden. With increased tissue temperature, the metabolism and therefore

the oxygen requirements rise This is not compensated by an increased speed of oxygen dissociation from hemoglobin with the result that gangrene may follow the application of heat Rest is indicated in the presence of wound gangrene or the appearance of rest pain Since trauma and infection impose greater demands for blood and the tendency to venous thromboses they should be carefully avoided Fungus infections in particular are responsible in many cases for the aggravations and complications in the disease Living in a warm climate is beneficial

Antibiotics are given for streptococcus infections and penicillin is injected if need be even intra arterially (Glasser et al) If fungus infections are present the patient should bathe his feet twice daily for thirty minutes in a 1 3000 solution of potassium permanganate or soak them in Dakin s solution or in a warm boric acid solution The same treatment is used if gangrene or ulcers exist The resistance of the body to infections and sepsis is much greater in thromboangiitis than it is in peripheral atherosclerosis

Without the indications for bed rest mentioned above the patient may be up and about although too much walking should be discouraged With severe pain the dependent position of the leg may bring relief This position however should not be maintained too long otherwise the formation of edema is favored which also impairs tissue nutrition

If patients walk more slowly than they usually do the pain appears either much later or not at all

Talcum and dusting powders should be used freely to keep the feet dry

The shoes should be comfortable and should be changed often The socks should be made of soft wool Bed socks are of value Constricting elastic bands (garters) should be avoided The nails should be carefully trimmed and meticulous care should be taken to avoid every injury The nails should not be trimmed too short and the cutting should be straight across In order to avoid ingrown toenails an important complication capable of producing serious consequences the patient or physician should file the surface of the nail of the big toe in order to relieve lateral pressure

The feet should be bathed at least twice daily they should be dried carefully with particular attention paid to the interdigital spaces If the skin is too dry lanolin should be used if perspiration exists talcum powder should be applied often The legs and feet should always be kept warm

Operative removal of bunions is prohibited for corns an ointment containing salicylic acid may be used but with great caution A callus should be treated with sandpaper The patient should not sit with his legs crossed Overeating should be avoided but no special diet is necessary

A fundamental rule in the therapy of thromboangiitis is strict abstinence from smoking The greatest stress must be laid on this advice It is a repeatedly confirmed fact that smoking even one cigarette not only increases blood pressure and heart rate but lowers skin temperature as well While there is no convincing proof that tobacco is an etiologic factor there is no doubt that smoking even a

few cigarettes may cause a severe relapse it may prevent wounds from healing and may cause new areas of gangrene to appear One observer followed 100 patients with thromboangiitis obliterans who stopped smoking for over 10 years The disease was completely arrested *in all cases (Silbert)* *It does not* suffice to tell the patient not to smoke The dangers of smoking must be explained in detail to the patient and he should be informed that gangrene and mutilating operations are avoidable only if smoking is completely omitted The detrimental effect of tobacco in peripheral vascular disease was known for many decades but the importance of this factor in the treatment of thromboangiitis obliterans has been appreciated only in the last 25 years

Heat Treatment The damage resulting from exposure to cold and the benefit of warm temperature was recognized early and led to the application of warmth by different means (diathermy sitz baths) The warm foot bath as well as the contrast bath and heat cradle were widely used although often with detrimental effects The damage done by heat applied directly to undernourished tissue was explained above It is far safer to attempt to dilate the vessels to stimulate and improve collateral circulation in the legs by immersing the healthy arms up to the elbows into water at 40 C or more simply by applying a heating pad to the abdomen

Active Vascular Exercise In order to improve collateral circulation Buerger introduced vascular exercise It has been widely used in the past The legs are at first elevated to an angle of about 60 degrees and kept in this way two to three minutes until blanching occurs This is best done if the back of an inverted chair is used for support The patient should then dangle the legs for three to five minutes until maximal flushing develops This procedure is repeated five times and at each of three or four daily sessions These exercises as well as the procedures discussed in the two following paragraphs are contraindicated if an infection or an open wound exists The value of this therapy has not however been proved

Passive Vascular Exercise Another method of physical therapy is called suction and pressure treatment The involved extremity is put into a hermetically sealed boot Alternately high and low pressure is introduced within the boot for the purpose of expelling blood from the vessels with the high pressure and drawing blood into the dilated vessels during the low pressure period Similar methods of treatment have been known for more than a century but recently were revived and improved The original very enthusiastic reports have given way to some skepticism concerning the value of this treatment Here again there is no proof of an improvement of blood flow

Based on the finding that venous compression if sufficiently prolonged causes a reactive hyperemia similar to that of arterial occlusion intermittent venous occlusion by means of a special apparatus was recommended for treatment of peripheral vascular disease Success with this treatment has been reported repeatedly although some authors are somewhat skeptical We find *no advantage* in using any of these methods in the treatment of thromboangiitis obliterans

Drugs This treatment is often neglected in favor of the methods discussed above Caution is in order If strong general vasodilators are used the blood flow in the diseased extremity may diminish for obvious reasons

Papaverine one of the most active vasodilators is hardly ever used in the treatment of peripheral vascular disease The vasodilating effect is slight if the drug is given orally Intravenous and intramuscular injection are more effective but the vasodilatation is evanescent

Much too rarely used in our opinion are preparations of theobromine or theophylline The vasodilating effect of these agents is small if given orally in the usual doses but they are powerful and the action is prolonged when given intravenously We feel that the most active drugs are aminophylline (theophylline with ethylenediamine) and theophylline sodium acetate We prefer the latter because no reactions follow its intravenous administration Five to ten ml of a 5 per cent solution are injected intravenously every day for 15 days The injection is performed slowly The improvement in some cases is astonishing The patients can walk farther without pain in the calves the leg feels warmer and wounds heal faster The series of injections can be repeated whenever indicated Apart from rare instances of idiosyncrasy no untoward results are seen even from prolonged treatment One begins with 5 ml and gives 1 more ml every day If the full dose of 10 ml stimulates the patient too much 6 or 8 ml are given If theophylline sodium acetate is not available aminophylline in the dose of 0 25 Gm is injected very slowly

Between the series of injections suppositories containing aminophylline may be used one suppository of 0 5 Gm once or twice daily

Many other measures are recommended but are much less useful

Since spontaneous gangrene of the extremities was believed to be associated with an increased viscosity of the blood infusions of sodium chloride to decrease this effect have been advised Later the injection of 150—300 ml of a 5 per cent sodium chloride solution was recommended for the same purpose (Silbert) Two to three injections are given weekly and continued for many months This treatment temporarily met with great popularity but has been abandoned in most places Chills hepatitis and venous thrombosis sometimes follow the injections

More success is obtained with injections of foreign protein particularly typhoid vaccine Triple typhoid vaccine (Lederle) or typhoid H antigen (Lilly) are used The doses must be small in order that chills or a steep rise of temperature with accompanying vasospasm be avoided The first dose is around 5 million organisms this dose is increased slowly in the following injections which are given every third to fourth day The injection is repeated only if the effects of the previous one have disappeared entirely The use of larger doses has been followed by arterial thrombosis presumably caused by vascular spasm during the chill (Allen and Smithwick)

Choline derivatives were also employed as vasodilators The original method of administration by the intravenous route has been abandoned because too

many untoward effects were noted Iontophoresis with acetyl beta methyl choline chloride (Mecholyl) has been used in some peripheral vascular diseases with little success Histamine iontophoresis has also been tried Priscoline (tolazoline) an adrenergic blocking substance is often used but this may cause cardiac pain

Repeatedly the *administration of muscle extracts and of insulin free* pancreatic extract *has been recommended The best known preparation* Depropranex *is given intramuscularly in doses of 2 ml twice weekly* Proof that *this treatment is beneficial* however is still lacking in our opinion

Based on reports of vasodilating action of estrogens and the observation that thromboangiitis obliterans is rare in women the use of estrogens was advocated Recently androgens were also reported to be of benefit Here again the opinions of authorities differ Benefit is reported by some no effect by others

Mild adrenergic blocking agents such as Ilidar (azapetine) may yield some effect when vasoconstriction exists Arlidine acts in a similar way

In the treatment of these cases it should not be forgotten that one of the most pleasant remedies for many patients and at the same time a very active vasodilator is alcohol It should be given often During an acute exacerbation with excruciating pain large doses may give more relief than any other drug and may tide the patient over a critical period

Surgical Measures For patients with intolerable pain crushing or blocking of nerves was recommended These procedures do not always help and as was pointed out *some of these patients have even required a chordotomy as the final possible therapeutic step after all other measures were unavailing*

Therapeutic sympathectomy is *done* only in selected cases It *should never* be performed following an acute exacerbation or in patients whose complaints are only of short duration One must be satisfied that arterial spasm contributes greatly to the clinical picture before undertaking it However the response to sympathetic block may be poor while sympathectomy helps Block may lead to damage of the cord and nerve roots It helps only for about 8 hours

Resection of the second third and fourth lumbar ganglia provides good results Vascular spasm is eliminated sweating is abolished and the legs become warmer In cases of gangrene it is well to avoid operation There is also no certainty of therapeutic success in intermittent claudication Preganglionic sympathectomy has been recommended as the most beneficial procedure (Adson) The necessity *and advantage of this operation in a given case should receive serious consideration* *This mortality is estimated to amount to about 2 per cent* The morbidity after the operation also deserves consideration The *tonus of the peripheral* vessels recurs after a few months and they show greater sensitivity to the action of adrenalin

In recent years surgical restoration of the lumen of arteries by extirpation of the occluded area and end to end anastomosis has been attempted

Periarterial sympathectomy recommended by Leriche was abandoned when it was shown that the vasoconstrictor nerves run with the peripheral mixed nerves and join the peripheral arteries segmentally

ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE

Atherosclerosis (arteriosclerosis obliterans senile gangrene endarteritis obliterans) is the most frequent peripheral vascular disease and as pointed out earlier with thromboangiitis obliterans comprises about 95 per cent of all peripheral vascular cases

Peripheral vascular disease of diabetes (diabetic gangrene) is often separated in the discussion of this subject but fundamentally it concerns the same pathologic anatomic subject and the clinical manifestations are identical The fact that the disease occurs in diabetic individuals however is responsible for its earlier appearance the poor tendency to heal once ulcerations are established and the frequency of secondary infection

Incidence

The disease usually is encountered in persons over 50 years of age but it may appear much earlier in diabetics Women with the exception of diabetics are less often affected than men the ratio being about 6 to 1 The condition is often unilateral The arms are rarely involved One third of the patients have hypertension

Pathology

The pathologic changes are those of atherosclerosis with the same manifestations and symptoms as discussed in previous chapters in connection with atherosclerosis in other parts of the body The frequent involvement of the arteries in the lower extremities as compared to the rarity of the condition in the upper extremities has often been the subject of discussion In general the atherosclerotic process increases with the distance from the heart The descending aorta shows more involvement than the ascending aorta the abdominal aorta is even more affected and atherosclerosis is most common in the lower legs This is not due to an increased blood pressure in the lower extremities as was long believed for the pressure differences between the upper and lower extremities are not great The upright posture of man is not responsible because the process is common in animals as a matter of interest the first case of intermittent claudication due to atherosclerosis was described in the horse by a veterinarian

Atherosclerosis of the leg arteries often is very pronounced although the patient is symptom free This is usually explained by the fact that the process has not as yet led to arterial occlusion, if this did happen the occlusion occurred so slowly that adequate time was available for the development of a collateral circulation

Atherosclerosis causes vascular occlusion by fibrosis or by thrombosis which may involve large or small arteries In 90 per cent of amputated legs two or more vessels are occluded

When symptoms and signs of ischemia appear (rest pain pretrophic pain) one or more vessels are completely occluded

Atheromatous debris from atheromatous patches in the aorta may cause peripheral embolism (Flory)

The veins are rarely involved and in contradistinction to thromboangiitis obliterans there is no evidence of inflammation This factor the intimal atherosclerosis and the absence of intimal proliferation permit the histologic differentiation from thromboangiitis obliterans

The clots undergo hyaline and fibrotic changes secondary calcification also occurs in time there is some recanalization The media is often thin due to degenerative processes

Symptoms and Signs

The complaints of the patient and the objective findings are very similar to those of thromboangiitis obliterans The picture is modified by the rarity of thrombophlebitis and by the minor role of arterial spasm Presumably this results from the absence of adventitial and periarterial inflammation and the absence of nerve involvement

Intermittent claudication is the most common complaint and often involves only the toe or the heel The pain may appear at night and at rest and may be relieved if the covers are removed and the leg is exposed to the cooler air of the room *Rest pain may also disappear if the legs are kept in a dependent position Patients often feel better if they walk at night when the pain appears and they are relieved if the upper end of the bed is elevated so that the legs are the lowest part of the body*

These spontaneous nocturnal pains should not be confused with the night cramps in the calf that were mentioned earlier

Paraesthesias are often present One of the earliest symptoms is fatigue and heaviness of the legs

Sudden aggravation occurs if an arterial thrombus forms Under these circumstances the picture varies Sometimes gangrene with intolerable pain may appear within a few days Other patients have redness and swelling of a toe or a part of the foot resulting in the development of an ulcer Sometimes there are no signs of impaired tissue nutrition but intermittent claudication and other complaints increase in intensity

Due to the development of collateral circulation slow spontaneous improvement of the condition is not rare

Even if the involved artery becomes occluded the paroxysms of rest pain particularly at night never reach the severity that characterizes thromboangiitis obliterans In the rare case of extreme *vasospasm petechiae develop in the lower leg* (Hines and Barker)

The signs are those of arterial occlusion and diminished blood supply to the extremity It is important to realize that patients with atherosclerosis of the leg arteries may complain of intermittent claudication without showing evidence of diminished blood supply in the superficial tissues

Gangrene may appear after a spontaneous thrombosis In most cases thrombosis of a peripheral atherosclerotic artery is the result of the rupture of a giant capillary in the intima as in coronary thrombosis Gangrene often follows the least trauma and infection

Roentgenologic demonstration of lime salt deposits in the vascular wall provides little help for the diagnosis It is sometimes not seen in spite of marked nutritional disturbances resulting from atherosclerosis In many cases it is very pronounced when the arteries are patent and circulation is normal Monckeberg s medial sclerosis does not disturb the blood supply to the tissues In this condition concentric incomplete rings are found while in atherosclerosis diffusely distributed placquelike densities are seen

Clinical Course

All variations are seen Within a few days gangrene may follow thrombosis in a patient without previous complaints in others a long duration of intermittent claudication over many years may be noted without complications or exacerbations Prognosis therefore is difficult In one series of patients with obliterative atherosclerosis of the leg vessels 54 6 per cent died after an interval of three years (Hines and Barker)

If accidental complications such as coronary occlusion or heart failure do not hasten the end progress of the condition may lead to gangrene Arrest of the disease is much rarer than in thromboangiitis obliterans and amputation are therefore more common

The separation of gangrenous parts from healthy tissues often takes many months It is astonishing how painless this is in some cases particularly when dry gangrene develops Cellulitis lymphangitis and other infections are common especially in diabetic patients

The appearance of atherosclerotic disturbances in the arteries of the legs in diabetics has been said by some to be independent of the severity of the diabetes its relative duration and even from therapy while others find it more commonly in neglected cases It appears in diabetics 10 times more often than in comparable age groups of controls

Treatment

The treatment consists of the same general hygiene and the avoidance of injurious factors such as excessive heat and cold trauma and fungus infections as discussed in the section on thromboangiitis obliterans Smoking is absolutely forbidden although abstinence does not prevent progression of the process The use of alcohol is permissible

A daily bath is enforced with cautious drying lanolin is used to soften the skin Corn pads may be worn but no local chemical applications are permissible

Among the various drugs mentioned in the preceding chapter only aminophylline (theophylline) in the form of suppositories and intravenous injections have yielded satisfactory results for us We wish to stress that we do not know of any other medical therapy that is equally efficient

Depropanex given once daily for the first week and then gradually less often has been recommended Its action may stem from its content of adenosine phosphate

The administration of anticoagulants is recommended for 2 to 3 weeks when thrombosis seems to threaten This event cannot however be predicted and the preventive power of anticoagulants appears doubtful to us since vascular thrombosis (like coronary thrombosis) seems often to be caused by rupture of a giant capillary in the atherosclerotic lesion

Blocking of nerves for the relief of pain is necessary much less often than in thromboangutis obliterans

The value of such various methods of physiotherapy as suction and pressure is even more debatable than it is in thromboangutis Postural active exercises are recommended

The appearance of gangrene or ulcers necessitates bathing the feet in solutions of permanganate or of boric acid The involved parts are kept dry with a mixture of 20 per cent boric acid and 80 per cent talcum

Opinions concerning the value of preganglionic sympathectomy are more divided than in thromboangutis obliterans Most observers are opposed to operation since the contribution of vascular spasm to the general picture is small in atherosclerosis Naturally the operation is performed in this disease only if the presence of arterial spasm is revealed by the measurement of temperature on the involved area before and after vasodilatation Gangrene has followed the operation despite the fact that skin temperature rose to 30 C after dilatation Return of vascular tone after operation is common It seems that postoperatively the vessels develop an increased sensitivity to adrenalin

De Bakey et al observed improvement in 85 per cent of patients without gangrene following sympathectomy Even with imminent gangrene extremities could be salvaged Major on the other hand found a significant improvement of intermittent claudication in only 9 of 54 patients following sympathectomy

In patients with intermittent claudication tenotomy of the tendon Achilles has been recommended Boyd et al had a good result in 22 of 24 patients and not one patient was unrelieved The operation is done subcutaneously The rationale is not clear Hamilton and Wilson had the operation performed with success in 4 of their patients

In segmental atherosclerotic occlusion resection of the involved part and replacement by autogenous vein grafts or homologous veins (saphenous superficial femoral) and bypass surgery has been attempted with success (Julian et al)

Mortality from operations is reduced with the use of refrigeration anesthesia

NARROWING AND THROMBOSIS OF THE INTERNAL CAROTID ARTERY

Thrombotic occlusion of the internal carotid artery of atherosclerotic origin is a common condition It has been found in 3 per cent of routine autopsies one observer found 45 such patients within two years The frequency of this condition was first stressed by Moniz et al

Men between the ages of 35 and 65 years provide most examples The patient experiences unilateral frontal headache pain around the eye nausea and vomiting Muscular weakness appears with drowsiness or temporary loss of consciousness or paresis in one arm or one side of the body Temporary hemihypesthesia or paraesthesia occurs as does complete but often temporary hemiplegia

Aphasia occurs In repeated attacks the same pattern is observed Tinitus paraesthesias and unilateral blurring of vision are noted Cataracts develop early total blindness may occur Facial atrophy may develop while convulsions with loss of consciousness and epileptic attacks have also been described The combination of homolateral blindness and contralateral cerebral lesions is characteristic

Palpation reveals the absence of pulsation of the internal carotid artery along the anterior border of the upper sternocleidomastoid muscle and in the fossa tonsillaris But even when pulsations are found the possibility of a thrombus situated higher up should be considered Most often the thrombosis is located at the origin of the artery

Men are more often affected than women The lesion occurs more often on the left side Both carotid arteries may be occluded by thrombi without consequences if the circle of Willis functions well

An arteriogram is rarely necessary and is not recommended because of the dangers involved

The course varies Some patients have only narrowing of the artery with attacks of the above described symptoms and signs coming on repeatedly over a period of many months Others die immediately after thrombosis of the artery

Anticoagulants should be given permanently to patients with incomplete occlusion

In several patients a successful resection of the thrombosed artery and direct anastomosis of the ends was performed (Denman et al Eastcott et al)

The first portion of the carotid artery is second to the abdominal aorta in it liability to atherosclerosis

ARTERIAL EMBOLISM AND THROMBOSIS

Etiology

Embolism of the arteries in the arm or leg occurs most often in patients with cardiac disease In patients with atrial fibrillation the emboli come *from thrombi* in the atria in one autopsy study it was found that 43 3 per cent of patients with rheumatic heart disease and atrial fibrillation had atrial thrombi (Garvin) Emboli often arise from thrombi in the left atrium e g in the course of mitral stenosis In myocardial lesions they originate from mural thrombi in the left ventricle

particularly in coronary disease with myomalacia and in myocarditis Cardiac disease was present in over 69 per cent of a series of cases with peripheral arterial embolism (Pearse) Emboli also arise from thrombi formed in aortic aneurysms or from atheromatous patches on the aorta

With a patent foramen ovale emboli are transferred into the greater circulation from thrombi originating in the pelvic veins or the veins of the lower extremities (paradoxical embolism) This phenomenon is not as rare as is commonly believed On two occasions one of us saw at necropsy the embolus caught just half way through the patent foramen ovale

Emboli usually impinge where arteries divide particularly at the bifurcation of the common femoral iliac brachial or popliteal arteries Embolism is particularly common in the posterior tibial artery

Additional (secondary) thrombus formation following an embolism is a common event It occurs mostly centripetally and may spread a long distance up the vessel and occlude the important collateral arteries

It is sometimes extremely difficult to differentiate primary arterial thrombosis from embolism If evidence of arterial occlusion appears in a patient with peripheral vascular sclerosis thrombosis is more probable Arterial embolism is more probable in patients with cardiac involvement Arterial thrombosis is occasionally seen in severe infectious diseases which frequently damage the vascular endothelium It is rarely observed following operations

Embolism in bacterial and subacute bacterial endocarditis was discussed earlier

Pathologic Physiology

The consequences of arterial occlusion by embolism and thrombosis depend upon the location of the occlusion and the availability of a collateral circulation The latter will develop easier with young elastic arteries than in peripheral atherosclerotic vessels of the aged

In many cases of peripheral arterial embolism the initial dramatic clinical picture observed disappears completely within a few hours Since the dissolution of the embolus is highly improbable presumably this improvement depends upon the disappearance of reflex arterial spasm which participates in the acute picture

If patent vessels are available effective collateral circulation may develop quickly for ligation of the main artery of a limb may be devoid of serious consequences A radial pulse following ligation of the brachial artery may reappear within a few days Embolism into the arteries of the upper extremities is rarely followed by gangrene

Complete interruption of the blood supply to the muscles leads to their death within 6 to 8 hours while nerve fibers survive for about 12 to 24 hours

Symptoms and Signs

Severe pain develops in many cases There is no certainty that the pain will develop immediately or after a short interval In all probability the original pain

is due to vascular spasm while pain appearing later is caused by ischemia Often the pain is excruciating and requires the administration of large doses of morphine but some patients have relatively little pain or even none at all In one series of peripheral arterial embolisms pain was reported in only 64 per cent of the cases in only 53 per cent did it appear immediately (Rykert and Graham) With the development of gangrene late pain is the rule In another study 59 5 per cent of the patients had sudden pain in 21 7 per cent numbness and coldness appeared suddenly and in 5 7 per cent the lesion was silent Those patients without early pain are in greater danger of losing the limb or a part of it because the situation is not realized at once and treatment is not started Time and again we have observed that the nursing staff paid no heed to the complaint of a patient about moderate pain in the lower leg and the physician was notified only after the lapse of many hours Peripheral embolism is diagnosed earlier if the nursing personnel and physicians are embolism conscious

With the pain or independent of it numbness and tingling with a pins and needles sensation appear in the involved part of the limb The affected limb feels cold

The affected extremities may show a very pronounced initial pallor particularly if there is much arterial spasm The cutaneous veins are empty Cyanosis may be present from the beginning unless the veins are empty Cyanosis together with mottling of the skin prevails in later stages Wheals and blebs may appear within 36 hours particularly when the surrounding temperature is warm

No peripheral pulse is found in the involved area The part feels cold and assumes the room temperature when exposed to it This coldness begins a few inches below the occlusion It should be emphasized that the involved limb may feel warm if it was well covered or if heat was applied to it Oscillometry shows no excursions and permits one to locate the occlusion Muscular paralysis appears within 30 minutes the sensory nerves are disturbed and the reflexes are diminished or absent

Fever with leukocytosis and an increased sedimentation rate appear The patient shows evidence of toxemia

Prognosis

It is estimated that recovery occurs in about 50 per cent of patients with embolism or thrombosis even without surgical intervention Spontaneous recovery was seen in 20 out of 36 cases (Rykert and Graham) of occlusion of the femoral or popliteal artery Owing to the seriousness of the general condition of the patient and the disease responsible for the embolism or thrombosis about 50 per cent of the cases in one series died within one month (Pearse)

Treatment

Opiates must be given to relieve the acute pain The involved extremity is kept warm but the application of heat should be avoided The ingestion of alcohol is useful In order to diminish the danger of secondary thrombosis heparin should

be started immediately Fifty milligrams are given intravenously every 5 to 6 hours

Collateral spasm is combatted by means of vasodilators Papaverine in the dose of 0 03—0 06 Gm is injected intravenously or into the artery of the involved extremity (Leiner) Theophylline or aminophylline is injected intravenously in the amount of 0 25—0 5 Gm

Paravertebral block epidural block or subarachnoid spinal anesthesia are used and often result in marked improvement

In cases without gangrene experience with these conservative measures shows that the results obtained are as good as with embolectomy In many cases however the development of gangrene cannot be prevented with conservative methods and therefore embolectomy will always retain its place Different opinions are expressed on whether the therapeutic procedure should be purely conservative or surgical In our opinion all the conservative measures discussed above should be instituted immediately If there is no sign of resumption of blood flow within six hours embolectomy should be done provided the underlying disease is one in which postoperative survival can be expected

If possible embolectomy should be done not later than 12 hours after the occlusion however successful operations have been performed after 24 hours The chances of full recovery are less with belated performance of the operation since the arterial endothelium is so damaged that arterial thrombosis may develop despite a successful embolectomy The problem is rendered difficult because it is not always easy to locate the site of the occlusion Symmetrical gangrene may be caused by a riding embolus at the bifurcation of the aorta or peripheral embolism in both lower extremities

Since the pioneer work of Key successful embolectomy has been repeatedly performed in every major hospital In one of our observations a riding embolism was diagnosed at the bifurcation of the aorta in a patient with a rheumatic mitral stenosis During the transportation to the operating room the embolus split into two parts and the patient developed signs of an embolism in the popliteal artery of one leg and in the femoral artery of the other The patient was operated on immediately by two surgeons one working on each side and survived the bilateral embolectomy When last seen she was in satisfactory condition and could walk without complaints

Sudden appearance of tingling in an extremity that previously was without sensation may indicate the recurrence of blood flow Observation with the capillary microscope may reveal the presence of a slight circulation and encourage conservative treatment

The opinions about the necessity for administering heparin are divided One group of observers gives heparin immediately another points out the dangers of embolectomy while a patient is under the influence of heparin Furthermore very serious and often lethal retroperitoneal hemorrhages have occurred when sympathetic block is performed during the administration of an

anticoagulant Therefore anticoagulants are only given if one is reasonably certain that no embolectomy will be done

OCCLUSION OF THE MESENTERIC VESSELS

Occlusion of the mesenteric vessels is a relatively common event especially in patients with atrial fibrillation bacterial endocarditis or atherosclerosis It may derive from either embolism which occurs particularly in the two conditions mentioned first or thrombosis Thrombosis is seen in atherosclerosis polycythemia infections and trauma Compression by tumor is also provocative Most frequently the superior mesenteric artery is involved The veins may also become thrombosed

Narrowing of the mesenteric arteries leads occasionally to the picture of abdominal angina the dyspraxia abdominalis intermittens arteriosclerotica of Ortner The pain is periumbilical and appears one to one and a half hours after eating i e at the height of digestion

In a venous occlusion prodromal signs may appear An arterial occlusion starts dramatically

An overwhelming steady and not colicky pain over the center of the abdomen appears and is accompanied by shock and vomiting In some cases the pain is less severe and patients with small emboli may survive at times without surgical intervention Infarction is not invariable Occasionally the symptoms are those of an acute intestinal obstruction or peritonitis Constipation or diarrhea is found Leukocytosis nausea and vomiting appear When serosanguinous fluid is found on peritoneal tap exploration is indicated (Mersheimer et al) The mortality even with an operation performed in time is about 90 per cent

OCCLUSION OF THE ABDOMINAL AORTA

Thrombotic or embolic occlusion of the aorta may produce a dramatic picture Few patients survive and death usually occurs within a few days Cases are recorded however in which patients recovered and records exist in which an old complete occlusion of the abdominal aorta above the bifurcation was an incidental finding at post mortem in some patients only intermittent claudication existed during life while in others no symptoms whatsoever were felt In still other cases the onset of symptoms may be insidious (Leriche syndrome)

According to Shapiro occlusion of the abdominal aorta is found once in 1000 autopsies It appears most often in males between 40 and 60 and rarely in younger subjects The patient complains of fatigue in the legs and pain around the hips and back on walking A systolic murmur may be heard over the abdominal aorta around the umbilicus (Covey) The lower extremities are cold and pale particularly when they are elevated

Femoral pulses and oscillations on the legs are absent Stable erection is impossible Wasting of one or both thighs occurs Thrombosis occurs in atherosclerosis while embolism is most common in rheumatic mitral stenosis Usually

they are combined since an original embolism usually leads to a secondary thrombosis The diagnosis of this condition and its separation from multiple embolism in the arterial tree often is very difficult

It is hard to explain how the collateral circulation is maintained in those patients who develop an occlusion of the lower abdominal aorta without symptoms Embolectomy has been successful in some cases

Patients may survive this syndrome for 10 years but sooner or later gangrene appears

Recently many successful attempts have been made to resect the thrombosed portion of the aorta followed by end to end anastomosis

SYNDROMES OF GANGRENE OF THE UPPER EXTREMITIES

Dead Fingers

So called dead fingers are not uncommon in otherwise healthy individuals The frequency of this phenomenon in the general population is estimated to be as high as 20 per cent The incidence is equal in both sexes

Often the patient suffered from chilblains in childhood With the onset of puberty (and sometimes in children no more than 8 years old) one or more fingers occasionally exhibit a cadaverous pallor usually beginning at the tip and spreading centrally the episode lasts for only a few minutes Numbness is present and tingling with pain is felt when the circulation returns There is redness due to vasodilatation the consequence of accumulated metabolites with the return of circulation The symptoms are sometimes symmetrical Rarely the toes are also involved

Usually the condition is hereditary sometimes it occurs in siblings It appears most often while the person is swimming in cold water Occasionally it develops without exposure to low temperatures but *it never occurs for emotional reasons and is never progressive* These two factors readily distinguish this phenomenon from Raynaud s syndrome

Rubbing and massage of the finger accelerates the return of the circulation in some cases

The condition is harmless and requires no treatment It may disappear spontaneously in the course of several years No nutritional disturbances are visible Hyperexcitability of the peripheral vessels which makes them react abnormally to cooling is considered the releasing cause

Raynaud s Disease and Phenomenon

The Raynaud *phenomenon* is sometimes found in periarteritis nodosa thromboangiitis obliterans (here rarely symmetrical) with cervical ribs in the scalenus anticus syndrome and other conditions discussed in the following pages One speaks of Raynaud s disease when an observation period over several years

reveals no etiology for the condition As opposed to Raynaud s phenomenon Raynaud s disease is usually symmetrical

Raynaud s phenomenon comprises cases of intermittent pallor and cyanosis on exposure to cold This is also a characteristic sign of Raynaud s disease Long after Maurice Raynaud s paper appeared it was shown that all but one of his cases actually belonged to another related group of lesions but his description is so classic that his name should be retained for this syndrome In order to avoid confusion however we will discuss here chiefly the condition which should bear the name Raynaud s disease

In the majority of cases it involves young women although it does occur in men (Hines and Christensen) There is also a hereditary factor Sometimes the patients are neuropathic but otherwise they are usually healthy In many patients the alterations may involve the toes as well

On sudden exposure to cold or on excitement a few or all fingers and some times even parts of the hand show a marked purple blue cyanosis or pallor Cyanosis is more common it has been shown that the waxy appearance of the fingers is found only if the blood is massaged out of the part flows out on elevation or is pressed out by reflex spasm Temporary return of the blood flow causes a pink color that quickly turns to blue if the circulation stops again The order of the color change stressed so strongly in the older literature on this subject is of no importance Pain may be excruciating particularly with the return of the normal circulation The involved parts of the extremities often perspire profusely

The excitement that initiates the attack may be a minor one Attacks may appear during ward rounds they may even be caused by a sudden knock on the door (Hunt) An attack may even appear if the patient sits quietly in a room with the temperature of only 18°C The critical temperature initiating an attack varies in different cases

The lesion is often progressive The attacks last longer and occur more often Sometimes the vascular spasm relaxes only after many hours Trophic disturbances develop in such cases There are small areas of necrosis in the skin over the fingers gangrene of large areas does not appear The skin becomes atrophic and there are disturbances of pigmentation The nails show trophic changes and decalcification with atrophy can be demonstrated early in the terminal phalanges by x ray Symmetrical gangrene appears

According to Raynaud the disease is a vasoneurosis resulting from a disturbance of the sympathetic nervous system It has been shown however that attacks also occur after interruption of the sympathetic nerve pathways The essential factor in most cases seems to be an abnormal excitability of the digital arteries to cold Participation of the smaller arterioles and venules in the spasm has not been demonstrated It has also been shown that it is possible to elicit the attacks regularly by exposing the fingers to water at a temperature between 15 and 18°C for 10 to 20 minutes (Lewis) If the hands are exposed to water under 10°C attacks do not occur Attacks appear however when the

body is cooled and the fingers are kept warm warming the body may relieve the attack

While the investigations by Lewis and his co workers make an abnormal reaction of the digital arteries most probable as an etiologic factor it is possible that an abnormal reaction to sympathetic impulses is important although the fact that the attacks may persist after sympathectomy speaks strongly in favor of Lewis conception

In typical Raynaud s disease there is no evidence of occlusion of larger arteries In more advanced stages intimal thickening of the digital arteries appears with secondary occlusion of small vessels partly by thrombosis and makes the appearance of nutritional disturbances and gangrene understandable With the narrowing of the lumen in these arteries even a slight increase in vascular tone on exposure to cold may interrupt the blood flow (Lewis)

With regard to therapy patients are advised to keep the hands warm and to avoid exposing other parts of the body to cooler temperature If possible the patients should move to a milder climate

Temporary improvement has been reported with ACTH and cortisone Priscoline (25—50 mg three times a day) and Roniacol help some patients

Cervical sympathectomy affords good results Even if the attacks recur after some time or remain they are milder shorter and less frequent Operations are inadvisable in very advanced stages when arterial obstruction is present The beneficial effect of neurosurgery proves that nervous factors play some part in the attacks The gradual reappearance of pain after the operation may be due to an increased sensitivity of the vessels to adrenalin following sympathectomy

Preganglionic operations are preferable in the upper extremities The rami of the second and third thoracic ganglia are divided In the lower extremities extirpation of the second and third lumbar ganglia is necessary Special care must be taken to avoid regeneration

Dermatomyositis may cause heliotrope color of the skin pigmentation asthenia and the Raynaud phenomenon It is occasionally associated with visceral disease which may precede the dermatomyositis Recovery may occur but usually the illness is fatal

In addition to the other syndromes leading to the appearance of Raynaud s phenomenon those due to the presence of cold agglutinins (Hausen) and cold precipitable proteins (cryoglobulinemia) occasionally encountered in myeloma should be mentioned (Barr et al)

Scleroderma

This is in many respects a mysterious disease of unknown etiology and one not susceptible to successful therapy Since it is often seen in patients with Raynaud s phenomenon it may be briefly discussed at this place

Although a differentiation is made between generalized scleroderma and the localized form (sclerodactyly acrosclerosis) it is not always possible to separate these conditions for one may merge into the other

The condition may start without vasomotor disturbances in other cases it begins after a typical Raynaud s syndrome For the most part it affects young females the ratio of incidence in the two sexes is 10 to 1 (Hunt)

The hands feet and face are usually involved the trunk is rarely affected The skin becomes shiny the normal wrinkles disappear and it is impossible to fold the skin at the finger tips Flexion and extension of the fingers become difficult the hair disappears the nails grow slowly and show trophic disturbances Sores and blisters appear at the tips of the tapering fingers

If the face is involved the masklike facies becomes devoid of expression The creases disappear and the mouth cannot be opened normally the eyes cannot be closed in advanced cases Disturbances of pigmentation appear Histologically there is hypertrophy of the collagen tissue which causes constriction of the blood vessels (Matsui)

With greater involvement of the skin there is considerable vascular constriction but the disturbed nutrition of the skin is not the primary causative factor since the condition often occurs without vascular disturbances moreover nutritional disturbances of other origin than Raynaud s fail to cause scleroderma

Perhaps the lesion is of toxic origin the possibility of an endocrine influence has been discussed Posterior pituitary extracts have been administered Often the process progresses very fast from the start and the prognosis is poor Patients become crippled since they are unable to move the fingers However patients may live with this illness in a tolerable condition over three decades

Myocardial fibrosis and dysphagia with esophageal strictures indicate that the process may be generalized in some cases The lungs kidneys adrenals pancreas larynx and tongue may also become involved although this is rare When affected these parts show fibroblastic proliferation

The disease may progress slowly Treatment is purely symptomatic Massage of the skin with olive oil brings some improvement Iontophoresis with mecholyl and histamine has been recommended Ganglionectomy is done and affords slight relief in cases in which a vasospastic component can be proved Other observers have obtained no success from the operation

Therapy with ACTH and cortisone causes temporary improvement Exacerbations during therapy with corticotropin have been noted (Lunseth et al) Treatment with veratrum alkaloids (1—3 mg of Veriloid three times daily) has been recommended (Fuller) Spontaneous remissions occur Patients often die from heart failure

Often *scleredema* is confused with scleroderma In the former the hands are not involved the skin is not atrophic and there is no depigmentation It is a benign self limited edema of the face arms and legs pleural and pericardial effusions occur

Acrosclerosis is separated from diffuse scleroderma only with difficulty There is swelling of the collagen fibers of the skin absorption of the terminal phalanges in the x ray and cutaneous ulcers and gangrene

Cervical Rib and Scalenus Anticus Syndrome Hyperabduction and Costoclavicular Syndrome

The occurrence of a cervical rib was known to Galen but disturbances caused by this abnormality have been recognized only in the last 70 years

Cervical rib is not a rare abnormality It may occur bilaterally The brachial plexus and the subclavian artery travel over the cervical rib laterally and downward

Cervical rib is more common in women than in men (Adson and Coffey) The first symptoms begin late (between the age of 25 and 50) presumably due to the fact that with advancing age the shoulder sags lower leading more readily to compression of the structures named above In right handed persons the right side is much more often involved than the left

The symptoms consist of burning pain sometimes of lancinating character felt mostly in the ulnar side of the arm and over the deltoid area Numbness tingling and some hyperesthesia appear The fingers and hand may be cold and discolored A bluish hue or redness appears in some cases while pallor is present in others There is abnormal perspiration and some swelling Muscular weakness may be followed by trophic changes and even gangrene The area of attachment of the scalenus muscle is often tender The blood pressure on the involved side may be lower

Sometimes x ray examination shows the presence of a cervical rib Lifting the shoulder may furnish temporary relief (Falconer and Weddell) whereas sudden rotation of the head or downward movement of the shoulder may cause pain

Opinions concerning the mechanism of the disturbances vary The original explanation which is still accepted by most authorities attributes the lesion merely to compression of the subclavian artery According to Lewis and Pickering damage of the endothelium leads to the formation of local thrombosis in the subclavian artery Migration of these thrombi to the periphery causes ulcers and gangrene of the fingers At post mortem one may actually find the subclavian artery imprisoned in dense bands (Oljenick) It is believed by some that irritation of the nerves also produces symptoms and signs Since the lancinating pain cannot be explained by a disturbed arterial blood supply irritation of the sympathetic nerves in the brachial plexus was considered a factor irritation with resultant vascular spasm was advanced as the cause of the syndrome (Telford and Stopford) The presence of excessive perspiration in the involved area speaks in favor of the latter conception In all probability a combination of these factors is significant

Surgical intervention is indicated if there is evidence that the complaints are progressive Resection of the cervical rib (if present) has been replaced by tenotomy of the scalenus anterior muscle at its attachment on the first or cervical rib (Adson and Coffey) The operation is usually but not invariably successful

Even in the absence of a cervical rib similar peripheral vascular phenomena may appear due to the fact that the subclavian vessels and the brachial plexus are situated in the angle formed by the attachment of the scalenus anterior muscle and the first rib the muscle or fibrotic bands may compress the artery and nerves under certain conditions (scalenus anticus syndrome) The deepest structure in the angle is the subclavian artery above it follow the eighth cervical and first dorsal nerves If a cervical rib is present the scalenus muscle inserts on it

In some cases particularly during deep inspiration the subclavian artery may be compressed between the clavicle and the ribs One type of paradoxical pulse results from this compression and in one personally observed patient a systolic murmur was heard over the subclavian artery in inspiration due to compression Hyperabduction of the arm for a long period e g sleeping on the hyperabducted arm may also compress the subclavian artery between the clavicle and first rib and seriously diminish the blood supply to the arm Pressure by crutches may cause a similar syndrome

Some Other Types of Gangrene

Syndromes associated with disturbed blood supply to the arms and productive of gangrene are observed in several other conditions that are often confused with the Raynaud syndrome

Ball Thrombus in the Left Atrium This condition is found exclusively in rheumatic mitral stenosis and causes a rather typical clinical picture with cyanosis and gangrene of the fingers toes the tip of the nose and ear It should be easily diagnosed and was discussed before

Infections Peripheral gangrene occurs following certain infections e g syphilis typhus meningococcus infection and infrequently in rheumatic fever

Intoxications Ergot and phenol may cause peripheral gangrene In some patients gangrene of fingers and toes has followed the injection of one ml of a standard ergot preparation used in the treatment of migraine or in obstetrics If the evaporation of phenol is prevented by a bandage local gangrene may follow

Symmetrical Gangrene of the Young Symmetrical Gangrene of the Old Rarely these conditions develop within a few days without apparent cause In the former an infection often precedes atherosclerosis or tuberculosis may be responsible in the latter But in young and in old patients symmetrical gangrene may develop in the absence of any other evidence of disease and particularly without signs of an infection or intoxication

In a 65 year old man of this group observed by one of us dry symmetrical gangrene developed on all fingertips within a few days There was no pain and no other evidence of disease

Hemoglobinuria Occasionally cold hemoglobinuria may cause symmetrical gangrene These patients usually have syphilis and may develop gangrene

after exposure to cold Damage of the vascular endothelium leads to arterial thrombosis

Diseases of the Central Nervous System In some diseases particularly in anterior poliomyelitis hemiplegia and syringomyelia disturbances of the circulation without gangrene are occasionally observed The peripheral circulation is abnormal if the limb is not used and muscles are inactive

Diseases Caused by Vibrating Tools Workers using vibrating tools pneumatic hammers pounding machines in shoe factories chisels and riveting machines may present a disturbance similar to Raynaud's syndrome These patients show evidence of a disturbed blood supply in the fingers and hands they are sensitive to cold and so forth The syndrome disappears quickly if the workers change their occupation when the first symptoms of the Raynaud phenomenon start But once established the condition usually persists even if the patient no longer uses such tools (Jepson) The pathophysiology is unknown The endothelium is not involved and therefore serious nutritional lesions are missing

Other Factors It may be mentioned again that in thromboangiitis obliterans as well as in peripheral atherosclerosis a Raynaud like syndrome is occasionally observed

Finally symmetrical gangrene has been seen in simple cardiac failure and has been explained by a reflex vasoconstriction (Perry and Davie)

Acrocyanosis

This condition formerly called a vasoneurosis appears almost exclusively in young women Whether an endocrine imbalance is responsible is unknown

The fingers and rarely the toes as well exhibit a marked cyanosis They feel cold and swollen particularly during the winter The patients also complain of excessive perspiration Fissures occur in the skin over the fingertips and the nails are altered Chilblains are common Pain is absent Cold aggravates the complaints and excessive warmth is also poorly tolerated In warm temperatures as well as when it is excessively cold the fingers are somewhat purple in color

In some instances the condition is purely symptomatic It occurs for example in thromboangiitis obliterans or after refrigeration

The mechanism is unknown Originally explained as an obstruction of venous drainage (Erben) it was believed later (Lewis and Landis) that the essential disturbance consists in an abnormal narrowing of the arterioles with widening of the capillaries and veins this diminishes the blood supply and causes oxygen deficiency in the vessels of the subpapillary plexus There is no vasomotor disturbance but only a local abnormal response in the arterioles Others assume that dilatation and lack of response in the capillaries and venules of the skin slows blood flow

The therapy is simple and consists merely in advising the patient to keep the hands warm

LIVEDO RETICULARIS

This condition characterized by mottled skin with focal bluish discoloration is recognized lately as a vascular disease It occurs mostly in women and involves the legs and feet Exacerbations occur in the summer months According to Feldaker et al 30 per cent of the patients have hypertension 50 per cent have emotional instability Particularly in cold weather numbness and pain appear vasospasm may be responsible but arterial occlusions are found Ulcerations of the skin gangrene and loss of the toes and limbs are reported Ganglion blocking agents (hexamethonium) and sympathectomy are recommended

ERYTHROMELALGIA

This condition was originally described by Mitchell in 1878 Believed to be a rare vascular disease it is currently assumed to be a syndrome common to several conditions and not an entity in itself (Lewis)

There is a unilateral (rarely bilateral) painful red swelling limited to a part of the extremity usually the leg The essential features are burning pain increased local heat increased pain on warming the involved area and on dependency improvement on cooling elevation and rest (Brown) The local heat has been explained by a dilatation of the arterioles the redness by a dilatation of capillaries and venules

According to Sir Thomas Lewis the condition is the result of an abnormal response of the arteries to warmth The skin is highly susceptible and sensitive to friction as well as to temperatures over 32°C The disturbance depends upon the liberation of a specific substance (histamine?) The name Erythralgia has been proposed (Lewis) Smith and Allen refer to it as Erythermalgia

A similar condition occurs after burns of the skin and is observed occasionally in polycythemia It is not rare in thromboangiitis obliterans

The therapy consists in keeping the involved area cool Good response has been observed after administration of epinephrine (Mufson) and the relief experienced after taking acetylsalicylic acid has been called specific (Smith and Allen) The condition may improve following sympathectomy

CAUSALGIA (REFLEX SYMPATHETIC DYSTROPHY) AND POST TRAUMATIC DISTURBANCES

Very painful circulatory disturbances are known to occur occasionally after trauma to a limb Mitchell called this condition causalgia owing to the burning character of the pain

Originally it was thought that the lesion was due to post traumatic spasm of the injured artery Vascular spasm from mechanical irritation is known to every physician The spastic vein which scarcely permits the introduction of a canula and the spastic artery met with in experiments on animals are well known to medical students Prolonged arterial spasm lasting for hours has been observed

following blunt trauma It was gradually recognized however that vasodilatation and not spasm is responsible for many of the symptoms and signs of causalgia and that nerve irritation alone without any trauma to an artery may be the essential factor

Prolonged bombardment of the spinal cord with pain impulses sets up a circle of reflexes similar to the painful disability of the shoulder in coronary disease These impulses spread via the connecting neurons of the internuncial pool up and down and across the spinal cord and set up disturbances in other segments The name reflex sympathetic dystrophy has been proposed since pain may be slight or missing

There is no parallelism between the severity of the condition and the degree of trauma The causalgic state may follow rather trivial trauma and it is estimated that some evidence of it occurs in about 5 per cent of cases after sprains The syndrome may begin hours after the trauma Because the original injury may be slight patients are treated as neurotics

The first sign is pain out of proportion to the injury The pain is continuous but it may also be intensified in paroxysms which last for hours In this stage there are no objective findings and the diagnosis of a compensation neurosis or malingering is often made Redness soon appears in the skin over the involved area and there is tenderness to touch and to friction The skin feels warm and later cold there is marked perspiration at this time The situation is similar to that found in erythromelalgia The pain may increase until it is excruciating and intractable Even chordotomy has been performed without benefit in these cases and it has been even suggested that the sensory cortical centers be removed

Presumably due to the vasodilatation and increased blood flow bone atrophy (Sudeck s atrophy) sets in (Leriche and Fontaine) the skin may be edematous and the muscles atrophic largely as the result of disuse

With respect to treatment everything must be done at the beginning of the syndrome to relieve the pain infiltration of the injured area with procaine has proved useful in more advanced stages paravertebral sympathetic block is recommended or finally preganglionic sympathectomy

Priscoline may be given in doses of 25—50 mg four or five times daily Cortisone and ACTH have been employed with some success Recently ganglion blocking agents (hexamethonium and dibenzyline) have been used with success (Fowler and Moser)

THE PULSELESS DISEASE

Definition The pulseless disease — maladie sans pouls or Takayashu s syndrome — concerns a clinical picture described more than a century ago in single observations It became a recognizable and well defined syndrome after Takayashu s description

Pathology Etiology Syphilis is a factor in some cases since syphilitic aortitis obstructs the orifices of the large vessels originating from the arch of the

aorta In most patients an angiitis has been found with intimal proliferation (Mangold and Roth) It has been called an angiitis obliterans Others discuss the possibility of a dysontogenesis (Trias de Bes et al) It is possible that the etiology varies from patient to patient

Symptoms Usually young women are affected although it has been observed in both sexes after the age of 50 The patients complain of headaches particularly if the head is moved backward There are attacks of fainting vertigo and loss of consciousness if the patient changes her position quickly The heaviness and pains in the arms on working may resemble intermittent claudication There is also an intermittent claudication of the muscles used in mastication Very often there is dimness of vision photophobia amblyopia and transient amaurosis cataract visual disturbances of various types up to complete blindness which may bring the patient originally to the ophthalmologist Coronary artery involvement is rare

Signs The most outstanding clinical sign is the absence of the pulse of the arteries of the aortic arch i e in one or both carotids left and right subclavian Sometimes in one artery or another a small pulse is present but it soon disappears Trophic disturbances have been described in the skin muscle and even the skeleton in areas with an abnormal blood supply An ulcerated nose and palate occur The blood pressure in the lower extremities is often increased Therefore and because of the presence of a collateral circulation involving deeper arteries (affecting the same vessels as in coarctation of the aorta only with a reversed direction of blood flow) one often speaks of the syndrome as an inverted coarctation Even crenation of the lower border of the ribs due to enlarged tortuous intercostal arteries has been described (Ask Upmark) A systolic diastolic machinery murmur can be heard in the supraclavicular area near the attachment of the sternocleidomastoid muscle due to the widened collaterals with great speed of blood flow

There are many findings when the eyes are examined Corneal opacities atrophy of the retina iris pallor of the fundus low pressure in the retinal vessel glaucoma and cataracts in particular appear

Course There is occasionally an acute form which soon causes death Often the disease progresses insidiously for a few years the longest known case lived 14 years (Ask Upmark) The prognosis is poor

Therapy is unknown Favorable experience with cortisone and ACTH remains to be secured

PERIARTERITIS NODOSA

Although periarteritis nodosa is an uncommon disorder it is by no means as rare as was formerly believed At the last count well over 1000 cases had been reported since the original observations of Kussmaul and Maier in 1866 With the publication of series rather than individual cases the number is rapidly mounting

There is increasing evidence to indicate that periarteritis nodosa is not a disease sui generis. With this convenient term several types of necrotizing panarteritis are designated. The uncertain nosologic status is reflected in the existence of approximately 20 synonyms of which periarteritis nodosa and polyarteritis nodosa are most commonly used with a gradual shift toward the latter.

Etiology

The cause of the disorder is unknown. Syphilis is not an etiologic factor although many of the early cases occurred in luetic individuals and the Wassermann reaction is occasionally positive. A filterable virus has been considered responsible in order to account for the epidemic appearance of periarteritis nodosa in lower animals but no supporting evidence has been obtained.

The disorder is likely to occur in individuals who have suffered from asthma, serum sickness, various infections, sulfonamide reactions and the like, and it seems probable that a hyperergic reaction is responsible. This suggestion finds experimental support in the production of the characteristic lesion in rabbits by repeated injections of horse serum. The relation to the changes found in rheumatic fever has been stressed repeatedly.

Under certain conditions an infectious or chemical agent may alter the response of the vascular wall so that it reacts abnormally to a variety of stimuli (allergic hyperergic response).

Periarteritis nodosa occurs at all ages but it is most common between the ages of 30 and 40. Nearly 70 per cent of those affected are males (Boyd).

Pathology

The arteries affected belong primarily to the muscular type and the size of the vessels involved ordinarily does not exceed that of the hepatic artery. The location of the lesion in a given vessel depends on the size of the artery and the presence of vasa vasorum. In the larger arteries changes are prominent at the junction of the media and the adventitia, but in small vessels the lesion may remain for the most part subintimal. It is the tendency of the process to involve the medio-adventitial junction that led to the name "periarteritis," while the fact that destruction of the elastica was often followed by aneurysmal outpouchings suggested the term "nodosa." Moreover the lesion is discontinuous and affects only limited sections of an artery.

The initial necrosis is followed by leukocytic infiltration, exudation and the development of granulation tissue. The elastic membranes are particularly susceptible and may be destroyed. If the inflammation extends through all layers of the vessel, the elastic layers are destroyed and the media is necrotic. Small aneurysmal nodules, firm, pinkish or red and varying in size from one to several millimeters, may be scattered irregularly along the affected artery. If the artery ruptures — a rather common event in the renal and perirenal structures — massive hemorrhage may result. In smaller vessels the major lesion may be subintimal.

in this case local thrombosis may result in occlusion of the vessel and an infarction of the tissues supplied by the artery an event not unusual in the mesenteric arteries and the intestine Irrespective of the location of the lesion in the adventitial or subintimal area the exudate is often composed largely of eosinophiles a fact which lends further support to the possibility of allergy as an important etiologic factor

There is a subacute phase with evidence of repair so that intimal proliferation may be found adjacent to medial necrosis Moreover a chronic state is seen in which the inflammatory processes have vanished in this instance the lumen of the vessel has usually been closed owing to proliferation of the intima and thrombosis while the media may show calcium deposits Since the affection is often characterized by exacerbations and remissions all kinds of lesions from fresh to healed may be observed at necropsy

Although the involvement of the veins is less common and much less conspicuous in occasional cases the participation of the venous system is prominent with the result that clinical as well as histologic similarities between periarteritis nodosa and thromboangiitis obliterans exist

Symptoms and Signs

The clinical picture is remarkably diversified since arteries in practically every region of the body may be affected in varying degrees either simultaneously, in sequence or individually Moreover the process acts with variable intensity on different arteries and even on a single artery thus mild involvement of a mesenteric artery may slightly interfere with the blood supply of a portion of the intestine and cause intermittent colicky pain Furthermore the intestine may be infarcted and fatal peritonitis develops with fulminating speed

Even the onset varies from insidious to violent Often a tonsillitis or some other infection precedes the illness by a few weeks or months Sometimes after the patient seems to have recovered from the preliminary illness a new syndrome either in a new guise or simulating the old illness gradually emerges There may be loss of weight leukocytosis and increased sedimentation rate

In the ordinary case the impression created at the onset is that of a subacute febrile disease without particular localization Typhoid fever miliary tuberculosis or subacute bacterial endocarditis are usually suspected but no confirmatory evidence of these diseases can be obtained The situation is equally confusing if the affection does seem to localize If there are pains in the muscles with eosinophilia and fever trichinosis may seem likely and leads to muscle biopsy if the pains recur in the joints and an erythema develops with obscure fever rheumatic fever may be simulated Not rarely the abdominal symptoms dominate the clinical picture the fever abdominal pain the leukocytosis and evidence of peritoneal irritation suggest an acute cholecystitis or appendicitis necessitating operative intervention Not only does the surgeon fail to recognize the situation but the pathologist may overlook the lesion in the specimen and to his embarrassment discover the typical process when the material is reviewed at the necropsy

In rare instances the surgeon has noted the presence of aneurysms of the hepatic or other abdominal arteries

The fever does not follow any special course it may be high low or absent Prolonged remissions may recur between febrile episodes We have repeatedly encountered an irregular temperature closely simulating Pel Ebstein fever of Hodgkin s disease

Since the manifestations are protean reference will be made only to some of the clinical prototypes and outstanding phenomena in the succeeding paragraphs

Skin In rare cases the affection seems limited to the cutaneous vessels This rather prolonged and relatively benign type is recognized with the appearance of livedo racemosa and nodules The livedo consists of a flash of lightning discoloration in which the vessels are thick elevated blue red and dendritic *In the meshes of the livedo eruptions of various types occur* Livedo racemosa may also occur in other diseases (see above) and must be associated with the nodules to be diagnostic

The nodules are isolated subcutaneous shiny round pinhead in size move able and painful At times the nodules are somewhat larger and may attain the size of a pea in the subcutaneous form These nodules may break down and form ulcers Recovery usually occurs in this form although it may be postponed for two or three years

Subcutaneous nodules occur in about 20 per cent of cases of periarteritis nodosa when the abnormal findings consist for the most part of these nodules the term periarteritis nodosa subcutanea is sometimes applied The nodules tend to appear in crops on various parts of the body although the extensor surfaces are the most common site The number of nodules present at a single time usually *does not exceed 50 The appearance of a crop of nodules often coincides with* a new bout of fever

Ordinarily the nodules disappear in the course of a few weeks if no ulcer develops If numerous or large arteries are involved cutaneous apoplexy may follow or multiple areas of gangrene may occur and even simulate Raynaud s disease (Freund)

With or without subcutaneous nodules crops of petechiae may be found Although a variety of erythematous eruptions may be encountered purpura of the Schoenlein Henoch type is the most common

Owing to the secondary anemia which often develops pallor may be pro *nounced This* is common and with the wasting observed in some patients led to the old name chlorotic marasmus Apart from the pigmentation following subcutaneous hemorrhages a discoloration of the skin resembling that of Addison s disease is occasionally seen

Muscles and Nerves The neuromyositic manifestations are very important and may be explained by the involvement of the vessels supplying muscles and nerves Polymyositis (Fahr) is extremely common and often the correct diagnosis is established when a muscle biopsy is secured for suspected trichinosis Any or all of the skeletal muscles may be affected It is common to consider the possibility

of a dermatomyositis when the cutaneous and muscle symptoms are prominent sometimes differential diagnosis is impossible

In addition to a polymyositis there is often a polyneuritis characterized by pain weakness nerve trunk tenderness disturbance of sensation atrophy and paralysis A peroneal forearm type is rather common If an acute febrile polymyositis and polyneuritis is accompanied by albuminuria periarteritis nodosa should be suspected

In a minority of patients occlusion of the deep muscle arteries occurs or the peripheral vessels of an extremity become occluded and the segment supplied becomes gangrenous In this form designated periarteritis nodosa mutilans the clinical picture may approximate that of thromboangiitis obliterans

Abdomen The arteries supplying any abdominal organ may be involved thus producing a variegated clinical picture Involvement of the mesenteric arteries may be responsible for colic alterations of the bowel habit intestinal infarction or peritonitis Sometimes symptoms typical of an appendicitis may antedate all other symptoms for several months In one personally observed case polyneuritis and polymyositis developed four months after the patient had recovered from an appendectomy her eosinophilia did not recede in the interim The vessels of the gall bladder are frequently involved so that operations are undertaken for cholecystitis Gastric ulcers are not infrequent and hemorrhage is not unusual Pancreatic involvement is not ordinarily detected by clinical methods but diabetes mellitus has developed in rare cases periarteritis nodosa is one of the few causes for infarction of the pancreas

Despite these and innumerable other possibilities the most common abdominal symptom in periarteritis nodosa is vague pain usually epigastric or shifting from left to right in the course of a subacute or prolonged febrile illness The diagnosis of periarteritis nodosa is suggested in these cases by the finding of a polyneuritis polymyositis albuminuria and eosinophilia At any moment an abdominal organ may be infarcted causing hemorrhage or peritonitis to develop

Kidneys Sooner or later in the course of most cases (80 per cent in our experience) the kidneys are affected The urine contains albumin casts and other evidence of a tubuloglomerular nephritis It is however the rapid development of hypertension in the course of a febrile disease that makes periarteritis nodosa a diagnostic possibility While the elevation of blood pressure is not limited to febrile patients its sudden appearance and rapid evolution in nearly 50 per cent of the patients makes it an important sign Rather often the urinary signs the edema of the extremities and the hypertension lead to the diagnosis of an acute nephritis naturally the differential diagnosis between nephritis and periarteritis nodosa may be impossible if the vascular lesion is limited to the kidney

In a small number of cases the outstanding symptom is hematuria Instances are known in which essential hematuria led to nephrectomy for severe and recurrent bleeding and periarteritis nodosa was discovered in the specimen removed This form in contrast to the type simulating nephritis has a relatively benign course

More catastrophic is a variety in which periarteritis nodosa affects the kidney vessels Rupture of these *interlobular arteries may be followed by perirenal* hematoma and collapse Hemorrhage is common in all forms of periarteritis nodosa and accounts for many instances of shock seen in this disease The diagnosis usually is not considered unless a mass suddenly develops in one or the other flank

Renal infarction is also very common and terminal uremia is the usual outcome of those patients not succumbing to a vascular accident

Heart Tachycardia out of proportion to the fever is often observed and militates against the diagnosis of typhoid fever In spite of the involvement of the coronary arteries angina pectoris is rather uncommon Sometimes the aneurysms of the coronary arteries in this disease resemble the beads of a rosary but some of the cases of multiple coronary artery aneurysm reported in very young children undoubtedly belong to the congenital miliary aneurysms resulting from malformations of the arteries rather than to periarteritis nodosa

When there is an irregular fever and cardiac murmurs develop as the result of cardiac dilatation and anemia the suspicion of a subacute bacterial endocarditis is almost inevitable This suspicion may be strengthened by the development of infarctions hematuria petechiae and the like The electrocardiogram may show evidence of myocardial damage but is not altered in any characteristic manner Myocardial infarction is uncommon despite the occurrence of multiple aneurysms of the coronary arteries Involvement of the pericardial vessels may cause an inexplicable pericarditis

Congestive heart failure often supervenes and is next to uremia the most common ending of fatal periarteritis nodosa

Lungs In a large number of instances the syndrome of periarteritis nodosa seems to emerge from a previous history of bronchial asthma Not infrequently there is definite evidence of an allergy and the development of an increasingly severe intractable bronchial asthma after some mild illness should raise the question of the possible presence of periarteritis nodosa It has been suggested that the diagnosis of periarteritis nodosa should be considered in cases of bronchial asthma with more than 15 per cent eosinophiles (Wilson and Alexander)

In many cases the persistent low grade fever together with indefinite chest signs make the diagnosis of pulmonary tuberculosis likely While x ray changes may occur in the lungs of patients with periarteritis nodosa they are not characteristic nor do they simulate those of tuberculosis The occurrence of pulmonary infarction and pulmonary inflammation may cause marked dyspnea and cyanosis during the course of the illness

Endocrine Glands The endocrine glands have not been thoroughly studied in periarteritis nodosa but case reports are sufficient to show that they may be involved Apart from the better known involvement of the pituitary (syndromes like Simmond s cachexia) and the adrenals (syndromes resembling Addison s disease) no special clinical prototypes have been described

Central Nervous System Symptoms and signs arising in the central nervous system are observed in a minority of cases As might be anticipated they are

subject to great variation Occasionally in a patient with periarteritis nodo a meningitis was diagnosed until a negative spinal fluid was obtained Epileptiform attacks occur Likewise a variety of neuropsychiatric syndromes have been reported in older patients suffering from periarteritis nodosa but none of them are characteristic

Eyes Albuminuric retinitis is exceedingly common detachment of the retina is occasionally observed and total loss of vision has been recorded Aneurysmal dilatation of small fundal vessels has been seen Any of the intrinsic or extrinsic muscles of the eye may become paralyzed

Laboratory Findings

Laboratory findings are sometimes of diagnostic help The secondary anemia of moderate intensity gives little assistance As a rule the white blood cell count ranges between 12 000 and 20 000 In contrast to typhoid fever leukopenia is exceptional The increase in the number of white blood cells is due to a polymorphonucleosis but the percentage of polymorphonuclear cells does not rise to that ordinarily seen in miliary tuberculosis At least 10 per cent of the patients suffering from periarteritis nodosa have a marked eosinophilia there are few diseases in which the percentage of eosinophiles may become so high In one personally observed case they reached 60 per cent of the white blood cells while even figures as high as 90 per cent have been reported

Differential Diagnosis

Many of the differential diagnostic problems have been mentioned in the preceding paragraphs Miliary tuberculosis typhoid fever trichinosis neuritis meningitis encephalitis cholecystitis angina pectoris appendicitis bronchial asthma myositis and sepsis are often diagnosed before the true nature of the disease is recognized The diagnosis is inferential until established by histologic sections obtained by biopsy or during the course of some surgical procedure Obscure fever weakness pallor polyneuritis polymyositis vague gastrointestinal disturbances signs of nephritis or hypertension subcutaneous nodules and eosinophilia constitute some of the suggestive symptoms and signs

Allergy hypersensitivity angiitis and serum sickness angiitis must be considered Loeffler s syndrome and temporal arteritis are related In allergic granulomatosis which is related to Loeffler s syndrome granulomatous nodules occur in the epicardium and mural endocardium Clinically fever asthma and signs of vascular disease appear in various organs (Churg and Strauss)

Prognosis

Since most reports have been published by pathologists and major emphasis has been placed upon the tissue alterations attention has been focused on the lethal nature of the affection However the reparative process is often clearly

evident and recovery presumably occurs more frequently than was formerly appreciated

In most cases the duration of life after the appearance of major symptoms is about four months In the event of some catastrophe e g intestinal perforation the clinical course may be measured in terms of days otherwise survival for one or two years is possible when vital organs happen to escape serious damage although this is a rather uncommon occurrence However we observed several cases in medical officers of the last war where the diagnosis had been unequivocally established by classical peripheral symptoms high eosinophilia and positive muscle biopsy in which recovery was more or less complete save for an extreme atherosclerosis of the vessels of the lower extremities The course of the cutaneous forms is often prolonged and recovery with more or less invalidism is not extremely rare The most common causes of death are nephritis cardiac failure perirenal hemorrhages bronchopneumonia or peritonitis

Treatment

Attempts to ascertain the action and exclusion of possible antigenic substances do not seem to have been undertaken With the greatly reduced use of the sulfonamides the incidence of the disease seems to be less A host of measures with a positive therapeutic effect has been suggested which by their very multiplicity implies that none of them has much actual value moreover practically none of the supposedly remedial agents seems very rational if the current theories of pathogenesis are correct Thus the arsphenamines were advocated although the lesion frequently developed during treatment with arsenicals The same holds for the sulfonamides which have also been employed for the experimental production of the lesion Generally speaking agents have seemed to be most beneficial when evidence of visceral involvement was slight that is in the forms known to be associated with spontaneous remission

Therapy in our experience is mainly supportive and symptomatic Blood transfusions may occasionally make the condition more tolerable Special diets a high vitamin diet for example have been advocated but in practice the presence or absence of intestinal or renal involvement will determine the nature of the food permissible

In recent years ACTH cortisone and related substances seem to provide marked improvements Cortisone (?00 mg on the first day and 200 mg daily for 5—6 weeks) or 100—150 mg of ACTH are at present the medicinal agents of choice Often the fever disappears after a few days of such therapy but relapses are common

TEMPORAL ARTERITIS

This disease of unknown etiology was described in 1934 (Horton et al) It affects patients over 50 years of age most are between 70 and 80 although one patient was only 23 years old Women are more often affected than men

It begins with malaise vomiting pain in the ears and in the temporal area of the affected side and fever up to 39 5 C There is anorexia severe nocturnal headache and weakness After a few weeks there is a definite periarteritis around the temporal artery although the vessel still pulsates Soon it becomes thrombosed and very sensitive to the touch The palpable nodules consist of the thrombosed vessel and the periarterial inflammatory tissue Mastication becomes very painful *Leukocytosis* appears

In rare cases other arteries are also involved One even speaks of a cranial arteritis in those instances in which these arteries but not the temporal artery are affected Ocular complications seem to occur in one third of the patients owing to involvement of the ophthalmic and retinal arteries Blindness and visual disturbances are possible consequences In one case of bilateral temporal arteritis total blindness appeared (Shannon and Solomon) Apparently the visual disturbances are permanent

The disease is self limited After four to twelve months the symptoms and signs gradually subside or at least fail to progress an occasional case with a more protracted course is encountered

The histologic picture is similar to that seen in periarteritis nodosa The lumen of the artery is filled by granulomatous tissue with giant cells At present nothing is known about the histologic findings in other arteries of the body

Treatment is mainly symptomatic Potassium iodide has been recommended and ACTH and cortisone induce temporary remissions

Dramatic improvement may appear if the involved segment of the temporal artery is removed even infiltration with novocaine aids temporarily

ARTERIOVENOUS ANASTOMOSES AND GLOMUS TUMOR

Congenital and acquired arteriovenous fistulas were discussed in a previous chapter At this juncture reference will be made to some peculiar short circuits between arteries and veins which were described in classic papers many years ago but failed to attract much attention from physiologists and clinicians until their part in pathology was discovered by Masson in 1924

The Normal Glomus

Anatomy Some of the digital arteries divide into two branches One takes the normal course and divides into arterioles and capillaries which transport the blood finally into the veins while another branch sends blood directly from the arterial side into a vein The anastomotic vessel the Sucquet Hoyer canal has a very thick wall and is slightly tortuous It has a longitudinal and circular layer of muscle The outer muscles may be completely replaced by epitheloid cells This vessel suddenly changes its character and joins wide veins to form a convolution covering and surrounding the anastomotic artery The veins have no muscular fibers and only a thin layer of endothelium There are many collagen fibers between

these vessels and many nonmedullated nerve fibers A capsule consisting of connective tissue surrounds the whole structure Such a unit was called a glomus by Masson after the glomus coccygeum which has a similar structure Sometimes four Sucquet Hoyer canals originate from a single anastomotic artery

The glomus is situated in the deepest layer of the corium particularly on the fingers the nail beds the toes hands the foot The number of these structures has been estimated to be up to 500 per square centimeter (Grant and Bland) but is certainly less

According to most investigators the glomus appears in the first year after birth but it has been found in an embryo of six months (Clara) Their number diminishes in old age (Popoff) They are not found in cold blooded animals

Physiology Our knowledge of their function is limited It is certain that an anastomotic artery can close or open if the need arises that is the blood can be directed in the normal way through the capillaries or it can be shunted into the glomi Therefore Hoyer thought that these structures might play a part in the regulation of temperature Experimental observations have been made which favor this conception (Grant and Bland Lewis and Pickering) When cold is applied to the skin the anastomosis opens and warm arterial blood flows into the venous convolution Whether the glomus plays any part in the regulation of blood pressure is not decided

The appearance of arterialized blood in the arm veins in the tropics observed early by Pobert Mayer the appearance of arterialized blood in the submaxillary vein during stimulation of the chorda tympani seen by Claude Bernard and other observations in kidney experiments are explained by these short circuits and support the assumption that such anastomoses occur also in other organs Arterio venous short circuits were observed in the scleral conjunctiva (Urbanek and Scherf)

In this connection it is of interest that epitheloid cells similar to those found in the glomus are seen in the wall of the afferent arteries of the glomeruli of the kidney

THE GLOMUS UNDER ABNORMAL CONDITIONS

The behavior of the glomus in peripheral vascular diseases has been studied (Popoff) Changes have been seen in peripheral atherosclerosis where the afferent arteries are sometimes found continuously patent This may explain why the affected extremity often is warmer than the normal one Fewer changes are found in thromboangiitis obliterans but certain symptoms and signs of this condition have been ascribed to an abnormal function of the glomus

It is a very interesting fact that the blood of the saphenous vein in patients with atherosclerosis of the leg arteries often is more arterialized than the blood of the basilic vein (Popoff) This finding has been frequently confirmed it may be due to the patency of afferent arteries of the glomus

Glomus Tumor

Small painful subcutaneous tubercles were described early but since Masson's study their relation to the glomus (glomus tumors) and their common occurrence has become more widely appreciated

These glomus tumors are small bluish nodules of firm consistency and exquisite sensitivity to touch Usually they are found at the same areas as normal glomus formations They appear most often on the fingers particularly in the nail bed but are occasionally seen in areas where the glomus is normally absent e g the arm thighs shoulder chest wall neck or the buttocks

The outstanding symptom is pain which may be extremely severe It may occur in spontaneous paroxysms (crises) or may be constant The patient is always on guard to avoid pressure on the structure The pain may spread over wide areas e g over the whole extremity Changes of temperature also cause pain Patients with the same structures but without pain are very rare (Lendrum and Mackey) Occasionally trophic disturbances are observed in the involved part of the body The finger containing a glomus tumor may be warmer and may flush or perspire Multiple tumors are occasionally seen Numerous instances have been reported in which the tumor appeared after a trauma in one patient shortly after the tip of the finger was crushed by the door of an automobile a glomus tumor appeared under the nail of this finger

The tumors are usually very small in size and measure only a few millimeters in diameter The measurements of one tumor however were 1 5×1 0×1 0 cm (Ottley) and in another the longest diameter was over 3 5 cm (Lendrum and Mackey)

Histologically the tumors show the characteristic structure of the normal glomus but the composition varies and individual parts of the glomus may be exaggerated Thus the tumors have been called angiomyoneuromas Masson differentiates between an angiomatous an epitheloid and a neuromatous tumor depending upon the tissue prevailing in the glomus structure

The tumors are not malignant They compress the neighboring structures and may cause circumscribed atrophy for example of the phalangeal bone Recurrence after incomplete removal of a tumor has been reported (Ottley)

Usually pain forces the removal of the tumor bringing complete cure The tumor is not sensitive to radiotherapy

PERNIO CHILBLAINS FROSTBITE IMMERSION FOOT

Apart from certain systemic reactions to cold characterized by profound shock or by paroxysmal hemoglobinuria there are several local syndromes to which brief reference should be made

Chilblains or pernio represent a mild inflammatory reaction developing after exposure to cold damp cold in particular They are related to trench foot a condition seen in soldiers whose feet are exposed to damp cold for several days This in turn is related to immersion foot which is encountered primarily in

survivors of shipwrecks when the feet have dangled in cold water for several days A somewhat similar syndrome has been described in men shipwrecked in tropical waters but in this instance other factors than cold are present

If cold is applied to the skin it leads at first to arteriolar constriction and then to marked hyperemia which is followed by itching swelling and wheal or flare formation due to the release of histamine like substances Very early often within a few hours vascular thrombi are formed from red blood cell debris which silts along the vessel There is some separation of the endothelium from the vascular wall Edema forms early Reactive inflammation blister formation ulcers and gangrene are found in more advanced or more severe cases

Cold is apt to produce effects where large areas of skin are supplied by relatively small vessels — the fingers toes nose and ears

Mild forms of this condition are rather common in adolescent women in temperate climates The lesions are situated above the malleoli the skin is tender when rubbed and swollen Many of these patients seem peculiarly sensitive to chilblains after a previous injury by cold and the burning itching tingling of pain may be associated with swelling from time to time Under these circumstances there may be some permanent alteration in the vessels or nerves that renders the individual susceptible to subsequent exposures to cold

In slightly more severe forms there may be scaling of the skin and even patches of gangrene which ultimately heal If the part is frozen edema and blister formation in addition to secondary infection precede necrosis or gangrene the dead part eventually sloughs off after a line of demarcation has formed

Those living in the Arctics do not suffer commonly from skin injuries consequent to exposure to cold Since they are fully aware of the dangers proper precautions are taken to avoid exposure In this connection it should be mentioned that exposure to cold involves a special danger in that lower temperature may produce local anesthesia and abolish the warning signals of impending freezing It is not the absolute temperature alone which is important but also the humidity of the air and the activity of the patient

Immersion foot may develop in a day or so after exposure The part is painful numbness and tingling is annoying There are no pulses in the arteries (Ungley et al) The swollen pallid skin contains cyanotic areas This is the so called prehyperemic stage Subsequently the pallor is replaced by erythema The feet become very warm but do not sweat Edema may obliterate the pulse which otherwise has become full again Pain is severe and continuous Vesicles containing straw colored or sanguinous fluid may form If local patches of gangrene develop they are usually not extensive and do not require more than amputation of toes The chief difference between frostbite and immersion foot consists in the fact that in the latter the tissues are chilled but not frozen

Until the last war it was recommended that the involved part of the body be kept cool and that only very slow thawing be permitted but since then it has been found that tissue damage is less when the involved extremity is warmed

as soon as possible The best temperature applied for thawing is around 40 C After thawing is completed warming is discontinued

Rubbing the affected area is forbidden since the entrance of infection into a blister abrasion or fissure may constitute a serious threat to life Pressure bandages tend to minimize the formation of edema Infection contributes greatly to the danger and must be controlled or prevented by measures which will not further injure the skin Therefore antibiotics should be given

The tropical form of immersion foot requires the additional management of vitamin deficiency and hypoproteinemia

Prophylactic measures prevent the appearance of chilblains and trench foot in most cases

DISEASE OF THE VEINS

Varicose Veins

Pathologic dilatation of veins may result from diffuse enlargement (phlebectasia) or unequal circumscribed dilatation (varicosities) While these phenomena may occur in the central nervous system the esophagus broad ligament urinary bladder spermatic veins and so forth reference will be limited to varices of the lower extremities

The actual incidence of varicose veins is unknown The usual estimate of 10 per cent in young healthy industrial workers is probably low since it concerns a selected group of adults

The etiology is equally obscure and it has been impossible to study the problem by animal experimentation The frequency of the disease in certain occupations (waitresses laundresses traffic policemen) that place a special burden on the legs and require the patient to stand for long periods is established The familial occurrence and the appearance in many members of the same family even in early youth emphasizes the significance of heredity A constitutional aspect is implied in the description of an asthenic type of individual with inherent weakness of the connective tissue The development of varices in the early stages of pregnancy before mechanical factors come into play suggests the participation of an endocrine influence the importance of increased abdominal pressure in the back flow of blood to the heart is demonstrated by the appearance of varicosities in patients engaged in hard labor

In general two factors a primary change of unknown nature in the vein wall and stasis seem to be of great importance

The early pathologic changes observed consist of dilatation elongation and tortuosity of the vessel associated with some hypertrophy An inflammatory reaction in and around the vessels is more or less constant but seems to be secondary to the stagnation of blood in sluggish pools rather than primary Thinning of the vein followed by saccular or spindle shaped dilatation begins near a valve and spreads distally Ultimately the continuous distention and perhaps infection lead to an infiltration of all layers of the vein by connective

tissue This rather characteristic fibrosis the genesis of which is entirely obscure may be followed by lime salt deposits (phlebosclerosis)

Symptoms The symptoms consist of fatigue of a drawing sensation and at times of pain Often these are early complaints evoking erroneous diagnoses This is particularly true when mere inspection does not permit recognition of the situation Sometimes there are cramps in the calves particularly at night or when the patient is in cold water Precordial pain dizziness and dyspnea occur because of pooling of blood in the lower extremities There is no parallelism between the extent of the varicosities and the number or severity of symptoms

Tests In order to ascertain whether the communicating veins function properly and are able to compensate for the abnormal circulation due to the varicosities certain tests are used In the Trendelenburg test the involved leg is elevated to empty the veins A tourniquet or cuff is applied about the upper thigh and the patient is allowed to stand If the veins remain empty or fill slowly (20—30 seconds) the test is considered negative if the veins fill rapidly (5—15 seconds) the test is positive In the latter instance the communicating veins are inefficient

Before undertaking any treatment to prevent the flow of blood in the superficial veins the physician should ascertain whether the deep veins are patent The simplest test is to apply an elastic bandage and ask the patient to walk Considerable discomfort appears if the deep veins are not patent

Perthes test is satisfactory for determining the patency of the deep veins The tourniquet is applied while the patient stands being placed just tight enough to prevent reflux from the saphenous vein The leg is then flexed and extended at the knee ten times or the patient may walk vigorously for a minute or two If the deep veins are patent and the communicating veins function normally blood is aspirated from the superficial veins and the varicosities collapse In the so called comparative tourniquet test the cuff is applied at different levels so as to determine the level at which the communicating veins are incompetent By this means one may demonstrate that low as well as high ligation is necessary If superficial *and* communicating veins are incompetent injections of sclerosing solutions are liable to be followed by recurrence of varicosities If only the saphenous vein valves are incompetent ligation followed by injections is usually not followed by a recurrence

In the Schwartz test the saphenous vein is percussed near its entrance into the femoral vein if the percussion wave is felt by the other hand which rests upon the varicose veins of the lower leg the valves are incompetent

Complications The complications created by varicose veins are numerous Besides thrombosis and thrombophlebitis a periphlebitis and suppuration may develop A varix may rupture externally or into the tissues The skin may become atrophic or pigmentation and eczema may appear when the varices have existed for a long time even elephantiasis may occur The notorious chronic varicose ulcer usually located on the inner side of the lower third of the leg may result from trivial trauma or may appear spontaneously These ulcers

are rarely painful but healing is associated with diffuse scar formation Edema of the ankle and leg is prone to develop if the patient stands for some time At any time an acute infection may occur with redness pain and increased swelling

Since the blood flows toward the periphery in a varicose vein pulmonary embolism is a rare occurrence following thrombosis

Varicose veins are almost useless for the circulation When the vein valves become incompetent the blood flows backward and toward the periphery in the varicosities The communicating veins alone conduct blood to the deep (femoral) veins which direct it to the heart The deep veins rarely become varicose owing to the support provided by the surrounding muscles they do however suffer not rarely from thrombosis and frequently are occluded when superficial varices are present If the communicating and the deep veins become affected and their valves become more incompetent intravenous and intracapillary pressure rises decidedly causing edema to appear This edema fluid is rich in proteins and leads to fibroelastic proliferation and induration Therefore one is justified in combatting it even with mercurial diuretics

Therapy In mild cases management should be limited to the application of an elastic bandage or the wearing of an elastic stocking

Formerly surgical procedures were the only method of treatment for marked varicose veins but later obliteration of the varix by injection became widely employed Recurrences are however common The method is based upon the fact that the intravenous injection of certain substances injures the vein wall to produce a phlebitis and local thrombosis with subsequent obliteration of the lumen Of the innumerable substances capable of producing an endophlebitis 5 per cent sodium morrhuate 15—30 per cent sodium chloride or 50 per cent dextrose are the most popular solutions they vary somewhat in efficiency the intensity of the local reaction and the amount of pain produced

The injection must be made with due regard for certain rules thus paravenous injection must be scrupulously avoided With many solutions meticulous care must be exercised since even a small amount in the paravenous tissues will result in a slough that may require excision and suture If there is any reason to suspect that some fluid has escaped from the vein novocaine should be injected immediately into the blanched area Moreover a bandage should be applied at the site of injection to lessen the chance of any leakage and to encourage adhesion of the vein walls With injections of sodium morrhuate anaphylactoid reactions occasionally occur particularly when a second series of injections is started after a rest period Unless the treatment is discontinued increasingly severe and even fatal reactions may occur A patch test has been advocated to determine sensitivity of the patient to the preparation

It is preferable to have the patient ambulatory except for a few minutes immediately after the injection this diminishes the possibility of embolism

There are many contraindications to injection therapy Among them severe cachexia advanced age, migratory phlebitis tuberculosis and the presence of intermittent claudication represent absolute contraindications equally impor

tant contraindications are a history of a cardiovascular accident hyperthyroidism and the presence of an acute infection of any sort

Injection therapy alone is done only when the Trendelenburg test is negative that is if the deep veins and communicating vessels are normal

Ligation of the saphenous vein and stripping of veins is a useful supplement when the valves of the saphenous vein are incompetent This is performed at the saphenofemoral junction and includes all tributaries of the saphenous at that point even if they are not dilated A similar operation is recommended in the presence of ulcers and brown indurated edema provided no infection is present Bed rest elastic bandages elevation and heat elastic adhesive dressings iontophoresis and numerous other procedures are available for the treatment of infected ulcers and should be employed before injection is undertaken

VENOUS THROMBOSIS AND THROMBOPHLEBITIS

Thrombosis

The importance of this process for the appearance of embolism its frequent occurrence and its dangers were discussed in a previous chapter A few further remarks seem relevant

Among the three factors regarded as responsible for thrombus formation — slowing of the blood stream chemical and physical alterations of the blood and injuries of the vascular wall — the first seems to be the least important Ligation of a vein at two points some distance from each other if done carefully to avoid endothelial damage causes a complete standstill of blood flow but no thrombosis Any trauma or surgical intervention may increase coagulability of the blood The susceptibility of patients with polycythemia to venous and arterial thrombosis is known The tendency of patients with fungus infections on the feet to thrombus formation was mentioned Dehydration also seems to be an established factor in increasing the likelihood of thrombus formation

Traumatic thrombosis may appear as late as 10 to 14 days after an injury The trauma may be trivial and often is forgotten by the patient A blow on the calf even by the relatively light object without the appearance of any visible alteration on the skin may cause a diffuse thrombosis of the deep veins Often the vein is not occluded by a thrombus but rather is compressed by fascia or an extravasal hemorrhage There is sudden sharp pain cyanosis and numbness

Heavy physical work may cause thrombosis of the axillary and subclavian veins with shoulder pain as well as cyanosis and edema of the arm (thrombose par effort) This accident is particularly common if the shoulder girdle is moved upward and backward without abduction of the arm Lifting a heavy object or pitching a baseball may cause this accident Injuries to the veins are common and may even cause them to rupture

Thrombophlebitis is more common in old age in carcinoma and in patients with varicose veins In rheumatic fever it occurs in the veins of the upper extremity and neck Aschoff bodies may be found in the walls of these veins

Prolonged sitting on poorly constructed seats may induce deep vein thrombosis. This was seen in the air raid shelters of London where the crossbars compressed the veins ("shelter legs"). Venous thrombosis occurs during flights in airplanes lasting for many hours. Compression of the calf veins by the weight of the leg in bedridden patients is thought to be responsible for the frequent occurrence of thrombi in these patients. On all these occasions mechanical compression of the veins may injure the endothelium and lead to thrombus formation.

In simple thrombosis the symptoms are very few or absent or are elicited only by careful inquiry. Pain in the plantar area of the foot, calf pain on dorsiflexion of the foot were mentioned earlier. Spontaneous pain is found only in a circumscribed area. It may not be superfluous to stress again that pressure and massage should be avoided. The spontaneous pain may be a mere soreness or it may be excruciating, particularly if a thrombophlebitis with perivascular inflammation is present. In ileofemoral thrombosis the pain may spread to the back.

It is estimated that deep vein thrombosis in the legs causes pulmonary emboli in one out of three cases. If these patients are ambulatory, walking upstairs may produce calf pain. Tenderness over the posterior part of the leg is almost always present. Swelling tends to be trivial and limited to the lower leg, but the thigh may be enlarged if the thrombosis extends to the femoral vein. The prophylaxis of venous thrombosis has been discussed earlier.

Venous thrombosis in the upper extremities is known as Paget Schroetter's syndrome. Males are usually affected. Among 300 instances it was found on the right side in 60 per cent (Hughes). Swelling, pain, sometimes discoloration, paraesthesias, and overdistended veins are found. There is often local tenderness. Anticoagulants and cervical sympathetic block are used.

Thrombophlebitis

The local symptoms of thrombophlebitis vary considerably with the particular vein involved. The usual picture will be recalled by mention of the familiar extensive thrombophlebitis of the legs, "phlegmasia alba dolens" or "milk leg" of older writers. Pain is felt in the medial part of the thigh. Both lower extremities are swollen, pale, and somewhat colder than normal. There may be moderate tenderness along the course of the deep femoral vessels. The local picture will be modified if, as often happens, the thrombosis extends into the external and common iliac veins or even into the inferior vena cava.

Fever accompanies thrombophlebitis. There is a leukocytosis and an increase of the erythrocytic sedimentation rate. If the inflamed area is superficial, inflammation is evidenced by the presence of a warm, red area, but if deep veins are involved the diagnosis may be difficult. Local signs are minimal or absent save for a small enlargement of the circumference of the calf if deep veins are affected.

The edema is partly due to increased capillary pressure Ligation of a large vein experimentally does not lead to edema and does not cause it clinically for there are too many collateral vessels If however many peripheral veins are obstructed edema develops This happens even in the absence of lymphadenitis and inflammation of the perivascular lymphatics Obstruction of major lymphatic trunks can however be a factor in the production of edema

The vasoconstrictor impulses arising from a thrombosed and inflamed vein cause arterial spasm and may even lead to gangrene (Homans) this is a common reason for the erroneous diagnosis of an organic arterial disease

Thrombosis of the veins of the upper extremities rarely causes pulmonary embolism In many cases the signs caused by pulmonary embolism lead to the diagnosis of pneumonia or pleurisy while the real situation is unrecognized

Perlow described as phlegmasia caerulea dolens a syndrome with shock and unconsciousness caused by the loss of about 5000 ml of plasma into the tissues There is severe cyanosis of the leg with petechiae and purpura Blood and plasma replacement may be life saving

Therapy In venous thrombosis and thrombophlebitis the local excruciating pain is often ameliorated by the application of three or four leeches in the neighborhood of the thrombosed vein area The treatment is ridiculed only by those who have never tried it in our experience the results have been very gratifying

In thrombophlebitis of the lower leg bed rest is indicated when acute inflammatory symptoms are present The inflammatory process subsides more rapidly by immobilization and the edema diminishes as the result of elevation Decrease of the edema is important since it tends to be a permanent feature if it persists for any length of time Restriction of fluids and of salt as well as the use of mercurial diuretics or calcium gluconate have been advocated to lessen edema formation The use of novocaine block to relieve veno and arterio spasm which are likewise considered important factors in the production and maintenance of edema is mentioned below

A difficult problem always faced is the duration of bed rest No standard period is known Prolonged recumbency offers just as much danger as premature walking The former may lead to the formation of new thrombi the latter to pulmonary embolism Unfortunately no reliable method is available to decide the best course in a given case In thrombosis of the femoral and pelvic veins bed rest must be prolonged four to five weeks The foot of the bed is put on blocks The patient is admonished to avoid deep breathing and straining at stool

Many physicians do not advocate bed rest at all unless acute inflammatory symptoms are present In our experience if there is much pain walking in the early stage of the disease greatly aggravates the swelling since the collateral veins and lymphatics are incompletely developed

For the arterial spasm paravertebral injection is beneficial and has been widely used since Leriche s recommendation It relieves pain and as mentioned

above edema It also restores arterial circulation If the sympathetic trunks are to be blocked this measure should be instituted early and should be repeated a few times

If pulmonary embolism is present and its recurrence seems likely, femoral vein ligation has been performed just distal to the entrance of the saphenous vein Some operators prefer to divide this vessel hoping thereby to interrupt impulses responsible for the vasospastic effects Even the inferior vena cava may be ligated if one has the impression that both femoral veins are thrombosed or if there is a thrombosis of the iliac vein The operation does not absolutely prevent the occurrence of embolism but greatly diminishes the risk These operations have been known to gynecologists for many years and were employed successfully in cases of gynecologic sepsis

If operations are performed in patients whose collateral pelvic veins are also occluded serious complications will follow

Therapy with anticoagulants is the method of choice and gradually replaces venous ligation This was discussed in the section on pulmonary embolism It is applicable in thrombophlebitis as well as in thrombosis

The value of trypsin given intramuscularly is still not established (Innerfield) Stein warmly recommends therapy with phenylbutazone

Chronic edema of the leg consequent to a femoral vein thrombophlebitis is often followed by persistent induration of the skin and subcutaneous tissues Subsequently pigmentation appears and the leg ultimately turns brown The indurated tissue does not pit on pressure but ulcers are prone to occur Pain is variable and at times very annoying Infection of the lymphatics and extravasation of serum containing large amounts of protein leads to the deposition of scar tissue which contributes to the blockade of veins and lymphatics The treatment of this complication requires limitation of activities avoidance of dependent position of the legs and the application of elastic bandages unless further measures are indicated for the ulcers Examination from time to time may disclose soft areas that may contain large varices demanding injection therapy

THROMBOPHLEBITIS MIGRANS

Thrombophlebitis migrans or migratory phlebitis is a painful phlebitis and periphlebitis which occurs mostly in males Short segments of veins usually 5—10 cm in length are affected The involvement is usually observed in subcutaneous veins but in rare cases the deep veins are also affected Every recurrence is accompanied by an increase of temperature general disturbance of well being and tachycardia The affected superficial veins are palpable as hard tender cords which show at first a light red color then a livid discoloration and finally a brownish hue The inflammation also involves neighboring tissues for a distance of 3—4 mm from the vein

Widely separated areas are affected One day a painful thrombosis of a short section of a foot vein appears On the next day week or month another

vein is involved at the elbow on the inner side of the forearm or in the neck Thrombosis may even spread into the cranial venous sinuses Most cases described as thrombosis of the coronary or pulmonary veins with angina pectoris were actually instances of pulmonary embolism These with all their manifestations and complications are not unusual in thrombophlebitis migrans

In an astonishing number of cases focal infection is observed and the process disappears when these foci are successfully eradicated Histologically a periphlebitis and thrombophlebitis similar to that seen in thromboangiitis obliterans is noted For some authors every case of thrombophlebitis migrans is simply a form of Buerger s disease although we do not share this opinion The arterial circulation should be watched carefully in every case of migratory phlebitis

The course may be protracted and the disease may last for decades In some cases observed by us the progress was stormy and hyperacute In a few weeks multiple emboli may lead to death On the other hand the process may disappear at any time

In a large number of cases migratory phlebitis accompanies carcinoma It has been repeatedly described as an early sign of pancreatic carcinoma We have seen it early in ovarian and gastric carcinoma The relationship is obscure In pancreatic carcinoma a relation may exist to the mucin production (Durham) Thrombophlebitis migrans was observed to disappear after surgical removal of the carcinoma

The therapy of choice is the administration of anticoagulants which must be continued for months Oral administration of butazolidine (phenylbutazone) has been recommended Three and one half grams are given in one week (Stein)

OCCLUSION OF THE SUPERIOR VENA CAVA

More than half of the cases of compression of the superior vena cava result from aneurysm of the aorta Another 25 per cent originate from carcinoma of the bronchi Thrombosis of the superior vena cava possibly the result of a phlebitis of unknown origin is sometimes seen in tuberculosis syphilis or pyogenic infection Occurring in cardiac patients with advanced decompensation it usually starts in the jugular veins and is propagated into the superior vena cava We observed it in one patient with thrombophlebitis migrans

Although thrombosis of the superior vena cava may occur at any age it seems to be most common in the fifth decade Nearly two thirds of the patients are males

The pathognomonic symptoms and signs are edema and cyanosis of the face neck and upper extremities aggravated in the recumbent position and relieved in the erect posture The venous pressure is increased in the arms while pressure is normal in the lower extremities Dilated collateral veins may be visible on the anterior chest wall within a short time The slow cerebral circulation may lead to dyspnea and hyperventilation Pleural effusion may develop as the result

of increased pressure in the azygos veins Headache aggravated by lying horizontally is not uncommon vertigo may be noted Somnolence is an occasional symptom Prominence of the eyes and staring may be conspicuous Tinnitus and deafness may occur but vanish with the development of a collateral circulation

The symptoms depend to a great extent both upon the rapidity with which thrombosis develops and the underlying disease If the former proceeds slowly and collaterals form rapidly many symptoms like cyanosis facial edema and so forth may be absent

The prognosis depends partly upon the associated disease and partly upon the relative rates of venous occlusion and the development of a collateral circulation The mortality rate is high Death usually occurs in a few months but survival for many decades is possible In one personally observed case the thrombosis followed an acute tonsillitis this patient was still alive after six years although he suffered from extreme vertigo when his position was changed suddenly We have seen tuberculous endophlebitis of the superior vena cava with occlusion unfold its picture in a matter of weeks sometimes there is a marked change of personality before death

In recent years surgery has provided great relief to patients with this syndrome The azygos vein has been grafted into the right atrium or with the aid of arterial grafts it has been anastomosed to an innominate vein and patent parts of the superior vena cava

OCCLUSION OF THE INFERIOR VENA CAVA

A thrombosis or thrombophlebitis in the course of an infectious disease occasionally causes an occlusion of the inferior vena cava More often this event is due to a thrombus propagated from another vein Most common in our experience is occlusion of the inferior vena cava by a renal new growth in which a large mass of neoplastic tissue ascends the inferior vena cava

When occlusion of the inferior vena cava complicates the terminal phase of some other disease the clinical picture need not be modified When symptoms develop at all they consist mainly of leg edema and edema of the back without ascites The urinary output may diminish Subsequently an extensive collateral circulation may develop in which the superficial veins of the abdominal wall participate However we have observed collateral circulations in which the deep veins of the abdominal wall alone acted vicariously for the occluded vena cava and the diagnosis was impossible since no collateral circulation was visible externally

Among the measures for symptomatic relief repeated venesection may possess great value It may not prolong life but it may relieve many annoying symptoms for 48 hours or more

From the standpoint of differential diagnosis the principal source of confusion has been to mistake occlusion of the inferior vena cava for Baumgarten's

syndrome of the paraumbilical veins In both a remarkable caput medusae may be present but otherwise there is little similarity The outstanding signs of Baumgarten s syndrome apart from the caput medusae and thrill is splenomegaly and at least in many cases the recurrent ascites moreover Baumgarten s syndrome in our experience is seen in young individuals of the asthenic habitus who frequently lack secondary sex characteristics

Suppurative pylephlebitis and its relationship to appendicitis and to liver abscess endophlebitis syphilitica of the hepatic veins (Chiari s disease) splenic vein thrombosis and its association with the Banti syndrome various types of portal vein thrombosis and particularly the relatively common form observed in connection with cirrhosis of the liver as well as many other diseases of the veins belong to the domain of Internal Medicine and are not discussed in this volume

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Chapter 31

Therapy

General Remarks

In this chapter some measures available for the treatment of cardiac diseases are reviewed. A large number of therapeutic procedures for special conditions have already been discussed in the preceding individual chapters. The agents serving especially for the management of cardiac failure will find consideration in the discussion which follows.

Cardiac failure and decompensation should not be treated exclusively with drugs. Rest and appropriate diet alone will restore compensation in many patients.

The method of treatment so popular in the past, consisting of complete digitalization and then dismissal of the patient until cardiac failure reappeared, has been properly abandoned. Such treatment can be compared to leaving a non-swimmer under water and lifting his head out of the water now and then to prevent complete asphyxia. The patient must be under continuous control; his activities must be planned and discussed in detail with him. Compensation must be maintained by the mode of living as well as by continuous administration of drugs.

When decompensation develops, an endeavor should be made to determine its cause. Knowledge of the precipitating factor helps greatly in treatment. Often the appearance of an arrhythmia, particularly atrial fibrillation, of an infection with hemolytic streptococci, pulmonary embolism, extra physical strain or undernutrition will precipitate cardiac failure. In all these instances it is possible for the situation to improve after the disappearance or elimination of the precipitating factor. After they have recovered from cardiac failure, these patients may have an efficient and fully compensated circulation for years.

Decompensation must be considered much more grave, however, if it develops from failure of a markedly dilated heart or a steadily progressive process such as coronary sclerosis. Under these circumstances there is not much prospect that the state of the patient will remain satisfactory without continuous treatment. But even in the latter instance decided improvement may occur if, in the case of an earlier infarction, collateral circulation develops and strong scars are formed in the myocardium. Therefore, even the symptoms and signs of advanced cardiac failure in coronary sclerosis should never lead to an absolutely poor prognosis.

Psychotherapy has considerable importance in the management of decompensated patients and should not be neglected. All encouraging features should

be stressed such terms as cardiac failure should be avoided in discussion with the patient The term congestion is less alarming The importance of preventing mental strain and nervous tension in patients with hypertension or coronary thrombosis was mentioned in the respective chapters

The removal of visible edema dyspnea or tachycardia is not the ultimate objective of therapy Many weeks of treatment sometimes are needed until the heart acquires sufficient reserve and the patient is in an optimal condition The disappearance of dyspnea or edema does not constitute the maximal benefit from treatment

A discussion of the sexual life of the patient ought not to be omitted because of a false sense of prudery Actually patients are often thankful that they were anticipated in this question which they may have hesitated to raise In cases of coronary disease many deaths during sexual intercourse could have been prevented if the patient had been told to take nitroglycerin before the act

Greatest attention should be devoted to the treatment and prevention of all infections It was shown in the chapter on myocarditis how often the heart muscle is involved in various infections Patients with advanced valvular lesions or severe hypertension remain compensated for years as long as the heart muscle is normal but the slightest impairment of the myocardium may lead to cardiac failure It is readily conceded that dental granuloma gingivitis and dental abscesses do not play the role ascribed them by some advocates of the doctrine of oral sepsis Nevertheless foci of this kind possess great and often underestimated significance in many cases

Medicine possesses no satisfactory test for estimating the functional capacity of the heart and none for the early diagnosis of decompensation All the innumerable tests described such as registration of the heart rate and the respiratory rate the blood pressure at rest and after measured work and all the recommended combinations of these tests have little value The least exertion may increase the pulse rate and blood pressure more in the otherwise healthy neurotic individual than in a decompensated patient A careful history and exact examination furnish much more information on the state of the circulation of the patient than any of the functional tests now available

DIGITALIS

No other drug employed in medicine has created a literature as voluminous as that of digitalis Numerous monographs and innumerable experimental and clinical papers have digitalis as their subject While much research has been done particularly in recent years on digitalis glycosides and on purification of the drug the clinical rules laid down by Withering still hold and have been little improved This does not reflect adversely on the scientific zeal of workers in all countries but merely proves how unusual the experience the excellent powers of observation and the remarkable descriptions of Withering

Chemistry

Among the many plants of the digitalis group the leaves of digitalis purpurea and of digitalis lanata are used almost exclusively at present as the source of digitalis preparations Digitalis lanata is a species of foxglove that has the advantages of easy cultivation and a large content of active glycosides

The digitalis glycosides are composed of an aglucone (genin) fraction and a sugar fraction The latter is important for the solubility of the glycoside and enables it to penetrate the cells The aglucone fraction has a phenanthrene structure similar to that of the sex hormones (sterols) and desoxycorticosterone and exerts the specific cardiac effect

The three glycosides isolated from the leaves of digitalis purpurea — digitoxin gitoxin and gitalin — are known to have precursors they are not genuine glycosides (Stoll) These have still not been isolated

From digitalis lanata three products digilanid A digilanid B and digilanid C have been isolated from these digitoxin gitoxin and digoxin are derived

Digitalis contains many other substances among them the saponins which promote absorption from the gastrointestinal tract

The isolation of pure crystalline products digitoxin from digitalis prupurea (digitaline Nativelle isolated as early as 1869) digoxin (isolated by Smith in 1930) and cedilanid from digitalis lanata makes possible the administration of pure products of known strength

Pharmacology

Action of the Heart Muscle Digitalis glycosides increase the contractility of the myocardium This is seen even in isolated muscle strips and may also be observed microscopically in fibers from the specific tissue Systole is strengthened and is more complete so that the heart empties better The heart muscle is enabled to overcome greater resistence and its absolute power is increased The minute volume may be doubled There also are some effects on the diastolic phase although they are not very pronounced in the mammalian heart The speed of relaxation is increased but diastolic size is not reduced The increased velocity of the contraction shortens the duration of systole and the refractory phase (Junkmann) The pump works quicker stronger and the piston of the pump goes deeper than before digitalization

The action of digitalis on actomyosin and adenosine triphosphate is not clear It is possible that the diminished amount of ATP (Wollenberger) in the heart of patients with thiamine deficiency or hyperthyroidism explains the poor effect of digitalis in these conditions Digitalis increases the glycogen content of the heart muscle and diminishes the amount of lactic acid According to Pothlin et al digitalis interferes with energy utilization and not with energy production Bing et al found that strophanthin does not affect oxygen consumption of the failing heart which remains normal According to Proctor et al digitalis influences the enzyme systems that regulate the level of adenosine triphosphate

In patients with heart failure digitalis leads to disappearance of congestion diminution of residual blood fall of atrial pressure lower venous pressure better nutrition of the tissues and finally to an increase of the cardiac reserve power The peripheral blood depots open partly due to the disappearance of edema and partly due to widening of the peripheral vessels by other mechanisms All these actions begin soon and bring about a remarkable improvement It is claimed that digitalis is ineffective in high output failure This is true in our opinion only if the causative factor (pulmonary pathology arteriovenous fistula etc) persists in great intensity

Action on the Vagus Digitalis glycosides increase the vagal inhibition of the heart This effect is not of central origin it has been explained by increased sensitivity of the receptors in the carotid sinus (Heymans et al) or by sensitization of the heart muscle to the (normal) vagal tone (Abdon and Nielson)

This heightening of vagal inhibition is beneficial It may slow the heart particularly in cases of atrial fibrillation where it slows the ventricles by inhibiting the atrioventricular conduction The contractility of the ventricles is not impaired by this vagal action since — as was pointed out before — there are no vagus fibers and therefore no direct vagal effects on the mammalian ventricle

The conduction of a stimulus over the heart is directly impaired by large doses of digitalis This effect is observed even in isolated muscle strips

Action on Blood Vessels Much has been written about the vascular effect of digitalis glycosides A general vasoconstriction particularly in the gastro intestinal tract seems to take place under certain conditions but not with doses comparable to those used in therapeutics This effect is also counteracted by the improved peripheral blood supply the result of the stronger and shortened systole The special situation of the coronary arteries will be discussed later

There is no proof of a direct diuretic effect on the kidneys Any increase in urinary output is the indirect consequence of the improvement of circulation

Action on the Normal Heart It is often maintained that digitalis does not affect the normal heart but this statement is certainly untrue It must be expected that the efficiency of the systolic contraction will not be remarkably increased if the heart works under normal conditions The minute volume cannot increase as long as the inflow of blood to the heart remains the same If toxic doses of digitalis are given to healthy individuals the minute volume falls a finding that could be anticipated in view of the toxic effects of large doses of digitalis on the heart muscle According to some authors the diminished output is due to peripheral factors (Dock and Tainter)

Fixation and Cumulation Digitalis is fixed in the heart (Hatcher) It is still present 28 days after administration of one large dose It has been estimated that the heart loses daily 3 to 7 per cent of the cumulative amount of digitoxin The binding of scilla and strophanthin is slight Friedman et al found that the renal excretion of digitoxin lasted 24 days It is significant that elderly patients excrete much smaller amounts

The digitalis glycosides cumulate Even very small doses may suddenly exert toxic effects when repeated often over a sufficient length of time Originally cumulation was explained by simple addition until it was shown that large sublethal doses of digitalis cause necrosis of the myocardial fibers This necrosis was seen first in 1904 but was completely forgotten until it was rediscovered in recent times It is not yet decided whether the necrosis is caused by a direct action of the digitalis on the myocardium or whether it is due to ischemia Digitalis in sublethal doses also causes hyaline necrosis in the aorta and in the walls of the renal and coronary arteries Degenerative changes have also been seen in the brain The necrosis and hyaline degeneration in the myocardium is situated around the papillary muscles in particular it is followed by secondary leukocytic infiltration We may assume that smaller doses of digitalis alter the myocardial cell without leading to histologic changes It is probable that the cumulation is due to the increased sensitivity of the myocardium altered by small doses of digitalis to additional doses

The heart was supposed to store more digitalis than any other organ However recent investigations with the embryonic duck heart as test object (Friedman et al) speak against this predilection The authors found the greatest concentration in the liver and kidneys It is interesting to note that the tissues of the rabbit (examined by Friedman s technique) do not retain digitalis as compared to the tissues of other animals Digitalis is fixed by the cat heart but not by the rat heart and even the cat heart does not fix more than other organs of this animal This should be a warning against drawing conclusions from one species to another

The maximum capacity for destroying digitalis is according to Friedman et al 50 micrograms daily This amount is the same whether 0 1 or 0 2 mg of digitoxin are given

Most of the digitalis administered is excreted by the urine (80 per cent) and feces in an inactive form Only traces of active substances are excreted

Using radioactive digitoxin Okita et al found minute amounts in the heart after 40 days

Electrocardiogram The digitalis glycosides cause visible effects in the electrocardiogram The shortening of systole can be measured in the electrocardiogram and may amount to 41 per cent (Berliner) Within a few hours a single large dose may depress the PS T segments and lower the T waves These changes may persist for more than three weeks after discontinuation of treatment (figure 114) Extrasystoles will be discussed later Digitalis also causes atrioventricular conduction disturbances In some hearts with a damaged myocardium they appear following small doses

In figure 115a a prolonged P P interval exists The tracing was obtained from a 56 year old patient with hypertension who had received 0 3 Gm of digitalis daily for 18 days in the form of tablets of powdered leaves The P P interval measured 0 32 second In lead I the third atrial stimulus is not conducted to the

ventricle the following conduction is shorter due to partial recovery (Wenckebach's period) The RS-T segments and T waves are displaced in a direction opposite to the main deflection, a typical digitalis effect Figure 115b was

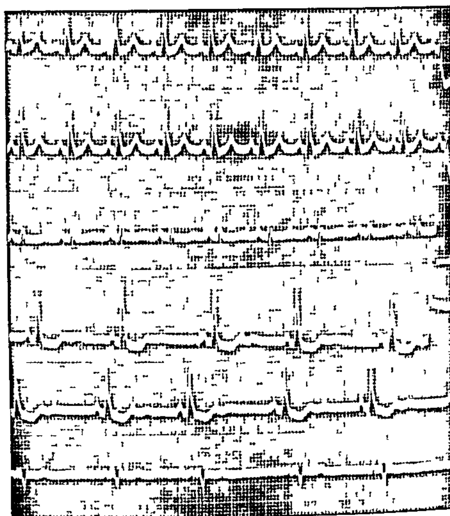


FIG 114 The upper three strips represent the three standard leads before, the lower 3 strips after digitalis therapy Note the change of rate and the depression of the RS-T segments with lowering of the T waves U waves appear this is common and may be explained by the diminished content of potassium in the heart muscle

taken from the same patient 17 days after digitalis had been discontinued The digitalis effects (conduction disturbances shortening of systole and RS-T changes) have disappeared

Standardization Methods for standardization of digitalis according to the amount necessary to cause standstill of the frog or cat heart in a given time

under certain experimental procedures are in wide use One should not forget however that preparations having the same strength experimentally (containing the same number of cat units) may have a quite different activity in men Even cat units cannot be compared with each other because of different methods used Likewise they cannot be compared to frog units since preparations having the same number of frog units may have different toxicity when tested in cats Therefore the labels indicating standardization of a preparation on frogs or cats may be somewhat misleading They often give a false sense of

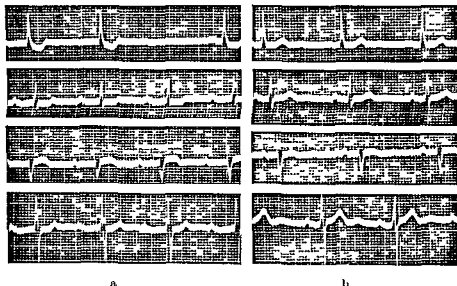


FIG 115 Atrioventricular block and deformation of the RS T segments and T waves caused by digitalis (a) Only left axis deviation remains 17 days after digitalis was discontinued (b)

security in dosage In a similar way standardization in man which has often been tried encounters great difficulties

Many preparations particularly tincture of digitalis deteriorate rapidly The pure glycosides do not require bioassay

Indications

Scientific evidence and reasoning often only superficially accurate cannot yet be conceded the final argument for or against the administration of digitalis in a special case The dose and mode of treatment must be determined by the real benefit the patient derives from it A long life is too short to learn enough about this wonderful drug (Wenckebach)

These sentences written by a great cardiologist illustrate clearly the superiority of practical experience over theoretical knowledge in digitalis treatment

Digitalis therapy is a great art that cannot be learned from books Only the inexperienced take it lightly Lives may be saved or astonishing improvement may be accomplished by a slight increase in dosage the addition or decrease of one tablet of 0 1 Gm of digitalis per day may change the whole picture

An exact knowledge of the indications and contraindications is the necessary basis for any therapeutic program with digitalis

There are two main indications for the treatment (1) evidence of cardiac failure (2) arrhythmias particularly atrial fibrillation with too rapid a ventricular rate

Cardiac Failure In the presence of rhythmic cardiac action evidence of myocardial failure is the only indication for digitalis Cardiac failure is evidenced not only by edema dyspnea and engorgement of the liver but also by Cheyne Stokes respiration nocturnal cough hydrothorax and pulmonary congestion Digitalization should not be postponed until cardiac weakness has fully developed The drug should be given at the first sign of myocardial failure

It has been stated that digitalis never helps patients with rhythmic cardiac action unless hypertrophy of the heart exists in combination with dilatation (Edens) Although no proof can be cited to support this statement there is some truth in it In concentric hypertrophy alone digitalis is not indicated and no help can be expected from it since the heart is not decompensated and no failure exists In patients with pure dilatation as in a case of toxic myocardial damage or following unusual strain digitalis is useless Digitalis is also useless in the myocardial necrosis of diphtheria and coronary sclerosis and in the myocardial damage of rheumatic fever Only if the basic condition or another disease in these cases (hypertension chronic coronary artery disease) has already led to hypertrophy and dilatation does the drug improve the condition of the patient

Digitalis is of course useless in congestive failure caused by pericarditis or cardiac tamponade Only in slowly developing myocardial failure as it actually happens in the majority of decompensated cardiac patients in whom hypertrophy and dilatation of some part are combined is digitalis useful

Digitalis is administered to these cases primarily for its positive inotropic effect that is to improve the contractile power of the heart muscle

In the presence of rhythmic cardiac action slowing of an accelerated cardiac rate (sinus tachycardia) by digitalis is often impossible If the tachycardia is caused by decompensation (Bainbridge reflex) it may disappear during digitalization (figure 114) but in many cases it persists unless toxic doses are used Thus in mitral stenosis with regular sinus rhythm and sinus tachycardia the rate remains rapid even if large doses of digitalis are administered In those patients who also exhibit marked pulmonary congestion digitalis is of little or no value because it does not help overcome the valvular defect and neither ventricle is incompetent Sometimes a tachycardia has a compensatory effect to maintain cardiac output as pointed out before

An increase of rate alone need not be the occasion for inaugurating digitalis therapy since cardiac acceleration occurs in the absence of decompensation

Thus considerable tachycardia may be encountered in a cardiac neurosis in hyperthyroidism in patients with aortic regurgitation in endo and myo carditis and other conditions without coexisting decompensation Often an entirely superfluous digitalis therapy is initiated in these patients It is on the other hand well known that digitalis often restores compensation without slowing the heart

Occasionally digitalis is withheld from decompensated patients even when they suffer nightly from attacks of paroxysmal dyspnea simply because the cardiac rate is slow One may encounter severely decompensated patients in whom the cardiac rate does not exceed 60 to 70 beats per minute Not rarely this happens to patients with coronary sclerosis in whom this bradycardiac decompensation may be due to abnormal nutrition of the sinus node It occurs in aortic stenosis The hesitancy to give digitalis in these patients is not justified The heart rate in these patients does not become slower during digitalis treatment and digitalization will cause marked improvement

Arrhythmias The second indication for digitalis therapy is seen even in the absence of cardiac failure it is represented by cases of atrial fibrillation and a rapid ventricular rate Here as pointed out before engorgement of the liver venous congestion and edema appear early when the ventricular rate is high In these cases impairment of conductivity by the direct action of digitalis on the specific tissue and via the vagus slows the ventricular rate to values between 70 and 80 beats per minute As soon as this level is reached the circulation is in an optimal condition Since with rare exceptions slowing occurs regularly with the employment of relatively small doses these patients react exceedingly well to digitalis Only a slight impairment of conductivity is necessary to prevent the majority of the weak stimuli originating in the fibrillating atrium from reaching the ventricle In rare cases atrial fibrillation may disappear during digitalis treatment even rarer are patients in whom the onset of fibrillation coincides with the treatment The special method of treating atrial flutter with digitalis has been discussed earlier

Other arrhythmias such as atrial extrasystoles and paroxysmal tachycardias are also abolished by digitalis but they respond better to other drugs e g quinidine

Other Indications Apart from the group of patients presenting cardiac failure and those with atrial fibrillation and flutter there are only rare indications for digitalis One is mentioned below in connection with heart block

The administration of digitalis in infectious diseases or preoperatively in order to strengthen the heart has been properly abandoned In these conditions peripheral circulatory failure rather than cardiac failure develops occasionally and digitalis is useless The administration of digitalis in pneumonia in the pre antibiotic era was abandoned after it was shown that there was no proof that routine administration of digitalis in these cases lowers the mortality It has also been recognized for a long time that cardiac weakness is not responsible for shock in this condition digitalis is therefore often without value

Contraindications

The contraindications to digitalis since they are so few may be summarized briefly Our claim that such contraindications are practically nonexistent is based on the fact that whenever the administration of digitalis is necessary it *must* be carried out since there is no substitute If cardiac failure is present or if the ventricular rate is too high in atrial fibrillation therapeutic success is not obtained without digitalis and the condition of the patient steadily deteriorates unless it is given Naturally there are patients in whom large doses of digitalis must be avoided but no contraindication to digitalis is admitted Allergy or intoxication signs mentioned below occasionally prevent continuation of treatment

For obvious reasons digitalis will not help in congestion of the liver and veins in pericardial diseases or cardiac tamponade nor will it abolish dyspnea due to pulmonary disease Even in patients with mitral stenosis and pulmonary congestion with sinus rhythm digitalis is not indicated and is useless

Since some older textbooks enumerate an entire series of contraindications they must receive some mention in this section

Paroxysmal Ventricular Tachycardia This disturbance — contrary to prevailing opinion — is a contraindication to digitalis therapy only when it appears during the administration of digitalis and is elicited by it Attacks of ventricular paroxysmal tachycardia not induced by digitalis are no contraindication and in fact respond favorably to it Thus we saw success in ventricular tachycardias following acute myocardial infarction even when quinidine was ineffective Scherf and Kisch observed a patient with attacks of ventricular tachycardia with alternating forms of ventricular complexes that always disappeared when digitalis was given

High Blood Pressure A warning was issued against digitalis therapy in the presence of an elevated blood pressure owing to the alleged danger of a further rise during the course of treatment The improved contractility and the shortening of the systole actually should lead to an increase of systolic blood pressure However so many regulating factors influence the level of the systolic blood pressure that at the bedside its height can always be disregarded in the question whether digitalis is necessary Often in decompensated hypertensive cardiac patients the blood pressure even falls during the course of the treatment of hypertension if decompensation was the cause of the hypertension (stasis hypertension) In other cases the blood pressure increases during digitalization But in these instances hypertension was present for a long time during the period of failure the blood pressure dropped but rose once again as digitalis therapy improved ventricular contractility

Embolism Patients who recently experienced an embolism in the lesser or greater circulation were often considered unsuitable for digitalis because of the fear that more powerful contractions of the heart induced by the drug might lead to the release of more thrombi and cause further embolism Any increase of

cardiac action due to a rapid movement or unavoidable excitement naturally offers the same danger Furthermore in these cases as in all others digitalis is given only when indicated therefore it must be administered since there is no drug with a different mode of action that can replace it

Coronary Disease Many physicians withhold digitalis from patients with angina pectoris and myocardial infarction In patients with anginal pain the detrimental effect due to narrowing of the coronary arteries is considered dangerous while in myocardial infarction rupture of the heart the result of more powerful contractions after digitalis is considered possible

Despite a tremendous amount of experimental work concerning the effect of digitalis (and strophanthin) on the coronary blood flow no decisive results have been obtained This is largely due to the fact that the coronary blood flow during digitalis therapy is influenced by factors which in many respects act oppositely The increase of cardiac contractility with shortening of the systole and the change of the heart rate may improve coronary blood flow while the increased vagus tone may diminish it A direct action of digitalis on the coronary vessels can only be studied in experiments on excised isolated vessels According to some investigators toxic doses narrow the coronary vessels No effect or only negligible reduction of blood flow is reported by others

Large doses of digitalis were given to 15 patients with angina pectoris and a positive exercise test i e marked changes in the electrocardiogram on exertion and in only one case did the complaints slightly increase in this single instance the alterations in the electrocardiogram became more pronounced on exertion after digitalis therapy (Hauser and Scherf)

Clinical experience shows that digitalis should be given if indicated to patients with angina pectoris due to coronary stenosis or patients with myocardial infarction

In cases of angina pectoris on effort the attacks occasionally disappear during the period of decompensation and reappear once compensation is restored This fact well known for many years has been questioned recently We have observed it repeatedly particularly in cases of aortitis and angina pectoris due to coronary stenosis The physician faces a dilemma and must choose between the Scylla of angina pectoris and the Charybdis of cardiac failure The disappearance of angina on effort in decompensation may be accounted for by the diminished activity of the patient due to dyspnea, edema and so forth But the fact that anginal pain at rest may also disappear has not as yet been satisfactorily explained

In coronary thrombosis with myocardial infarction the appearance of pulmonary congestion alone especially in the first few days is no indication for digitalis One will often succeed in preventing pulmonary edema and abolishing dyspnea by means of small doses of morphine and the congestion will disappear within a few days If however the signs of congestion increase despite morphine or if gallop rhythm and other signs of myocardial damage appear digitalis must be given The effect here often is as miraculous as in other cases Digitalis may

be particularly necessary in patients with a second or third attack of myocardial infarction or patients with chronic hypertension who develop myocardial infarction

Heart Block Cases of heart block (atrioventricular block) are often cited as unsuitable for digitalis therapy because of the danger of further cardiac slowing If complete atrioventricular block is present this fear is groundless since digitalis does not reduce the automatism of the ventricular centers but rather augments it if proper dosage is used Accordingly patients with heart block and a ventricular rate even as low as 20—30 may be digitalized without danger In patients with an incomplete heart block digitalis therapy may lead to a complete interruption of the atrioventricular conduction This event represents a lesser evil than non digitalization of a failing heart In fact digitalis is prescribed in atrial fibrillation for the purpose of impairing atrioventricular conduction and producing heart block Therefore cautious administration of digitalis in cases of heart block is permissible and even indicated when continuous change from partial to complete A V block causes Stokes Adams attacks

Signs of Intoxication and Side Effects of Digitalis Treatment

While true contraindications to digitalis treatment do not exist in some cases the administration of the drug must be interrupted even if its continuation seems indicated Interestingly enough many of these signs of intoxication and side effects of digitalis therapy were known to Withering

Allergy The administration of digitalis is sometimes impossible because of allergy to the drug Instances of scarlatiniform rashes urticaria asthma pruritus edema of the face and fever caused by digitalis have been described Rarely we have also seen skin rashes appear during the administration of strophanthin

Nausea and Vomiting Digitalis vomiting is not the result of direct irritation of the gastric muscosa since vomiting occurs on parenteral administration nor is it due to irritation of the vomiting center Some investigators considered reflexes emerging from the heart and running predominantly over the vagus responsible while others assumed that reflexes from the liver or other abdominal viscera cause it Vomiting has been observed however even after extensive severance of connections between the heart and the abdominal organs from the central nervous system Digitalis is said to have a central emetic effect which summates the effects caused by stimulation of peripheral reflexes outside the intestine (Borison) The oral administration of galenic preparations may cause direct irritation of the stomach by virtue of the saponins and other ballast substances

The vomiting often comes in waves with periods of relative wellbeing between them

If vomiting occurs during the course of digitalis treatment one possibility should always be considered namely that the doses administered are too small

to control the failure and the vomiting is due to hepatic enlargement and congestion This type of vomiting naturally vanishes if therapy is continued with adequate doses of the drug

Digitalis vomiting does not depend solely on the dosage It occurs in some patients even after small amounts of digitalis while in others relatively large amounts fail to induce it Therefore one is not permitted to consider the appearance of vomiting as a sign that the patient is fully digitalized

Anorexia nausea and diarrhea may also occur

Salivation Fatigue and Other Signs Neuralgic symptoms with shooting pains tingling of the fingers and generalized muscular pains have been described (Batterman and Gutner) Delirium may appear (Duroziez King) caused by injury to nerve cells Gynecomastia is found because of the action of the aglucones (LeWinn)

Other untoward effects described by Withering are increased salivation and great lassitude The latter appears particularly in elderly patients who also suffer occasionally from headaches delirium hallucinations and convulsions

Visual Disturbances Green and yellow vision is common blue and red vision is rare Dimness of vision inability to focus scotomata and even temporary blindness are occasionally observed

Eosinophilia A marked eosinophilia appears in the blood in some patients allegedly through an increase of vagal tonus (Pecht Romano and Geiger) Up to 30 per cent eosinophiles have been observed during digitalization

Anuria Anuria due to digitalis is rare but undoubtedly occurs In one of our patients with lead poisoning hypertension and nephrosclerosis the administration of four tablets of 0 1 Gm digitalis daily led to oliguria and water retention After the drug was discontinued for 2 or 3 days there was a profuse diuresis and a weight loss amounting to 5 Kg The experiment was repeated a few times with the same result Intravenous injection of ¼ mg of strophanthin daily had the same effect (Hauser and Scherf)

Coagulation of Blood In therapeutic doses digitalis was said to alter the coagulability of the blood With no change in the prothrombin time coagulation time was shortened (Massie et al) The frequent occurrence of venous thrombosis in cardiac cases has been ascribed to this effect of digitalis This effect of digitalis on the coagulation time has been denied recently (Sokoloff and Ferrer) but fast energetic digitalization is still said to increase the incidence of thromboembolism (Cormsen)

Extrasystoles Experimentally cardiac irregularities appear in cats after 75 per cent of the fatal dose of digitoxin and 60 per cent of the fatal dose of oubaine are given This includes conduction disturbances (Krueger and Unna)

A very important sign of so called digitalis intoxication is the appearance of extrasystoles They are usually found as bigeminy that is every normal beat is followed by an extrasystole We put intoxication in quotation marks because healthy mammalian hearts do not develop the regular digitalis bigeminy even when treated with toxic doses It was not possible to observe this disturbance

of rhythm in man following the administration of toxic doses (suicides) or in animal experiments as long as the heart was in good condition Only the dying heart may show bigeminal groups in the very last minutes before standstill Extrasystoles like those observed in the cardiac patient which may persist for weeks are obtained experimentally however if the myocardium is chemically or mechanically damaged (Kobacker and Scherf) In a similar way digitalis causes extrasystoles in patients only if myocardial damage coexists The nature of this myocardial damage the necessary prerequisite was unknown until recently If extrasystoles develop during digitalis therapy in a cardiac patient it indicates that the heart muscle is abnormal Accordingly the prognosis is always dubious

Recent investigations show that a diminished amount of potassium in the heart muscle cells is responsible Skeletal and heart muscle lose some potassium when fatigued Toxic doses of digitalis have the same effect whether the therapeutic doses do so is not certain but possible The potassium content of the heart muscle was found diminished particularly in mitral lesions with chronic heart failure (Calhoun et al) it is usually in these hearts that digitalis bigeminy appears Lown could elicit digitalis extrasystoles when potassium was removed from the serum by hemodialysis and Page could precipitate ventricular arrhythmias in 7 of 37 digitalized patients by reducing the potassium level in the serum through the administration of carbohydrates Anoxia acidosis adrenalin insulin and glucose injections increase the potassium deficit in the heart Since it is not only the amount of digitalis but also the state of the heart muscle that is important for the development of these extrasystoles the term sign of intoxication in the usual sense is not entirely justified Some patients do not develop digitalis extrasystoles even if they take 0 2 Gm of standardized leaf daily for years while others develop them regularly after the third *tablet* of 0 1 Gm digitalis (personal observations) Five to seven grams of potassium chloride daily in fruit juice abolish these extrasystoles

Extrasystoles and bigeminal rhythm may occur in cardiac patients independent of digitalis treatment In these cases digitalis therapy — if indicated — is permissible and one will usually find that the extrasystoles disappear during the treatment In patients who show extrasystoles in the course of digitalis therapy however great caution should be observed before further doses of the remedy are administered If the treatment is continued in the presence of extrasystoles caused by digitalis the number of extrasystoles often increases resulting in the development of threatening tachycardias and even ventricular fibrillation If digitalis treatment seems necessary one may continue the treatment with small doses i e not more than 0 15 Gm daily The patient must be examined at least twice daily and the treatment must be discontinued if the number of extrasystoles increases Most — if not all — deaths due to the administration of digitalis are caused by the neglect of this rule In an advanced stage digitalis extrasystoles occur so irregularly and so rapidly that an anarchie ventriculaire appears (Mahaim) the examining physician is convinced that

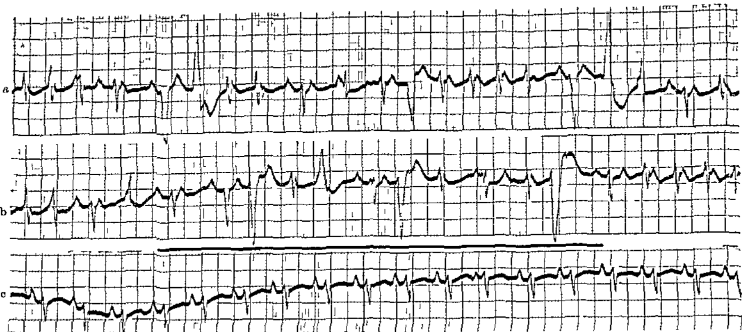


FIG 116 The top tracing (lead II) shows an atrial ectopic tachycardia and partial A V block in a 70 year old woman who had received 1 mg of digitoxin as a single dose Ventricular extrasystoles are also present In (b) the tachycardia remains during carotid pressure (the horizontal black line indicates the duration of pressure) it persists when pressure is discontinued Figure 116c shows a regular sinus rhythm interrupted by a single atrial extrasystole 11 days *after the digitalis* had been stopped and after the administration of potassium

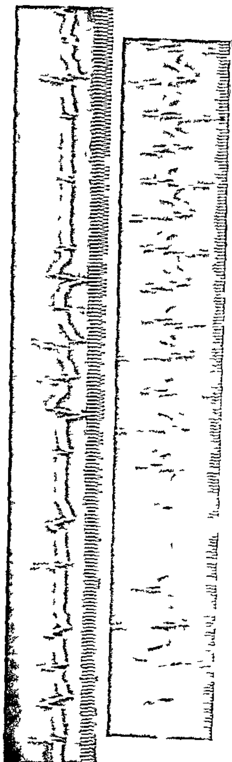


Fig 117 Fig 118

Fig 117 Atrial fibrillation and multiform ventricular extrasystoles with abnormal idioventricular ectopic beats caused by digitalis

Fig 118 Ventricular tachycardia with alternating form of ventricular complexes caused by digitalis There is also atrial fibrillation

he is dealing with atrial fibrillation and rapid ventricular action he increases the dose of digitalis and ventricular fibrillation is induced The principal reason that *the treatment with full therapeutic doses* — the administration of large amounts of digitalis in one or two doses — should be completely abandoned is that one can never predict after what dose of digitalis extrasystoles will appear Since they may develop even after a few *tablets* the administration of large initial doses may lead to dangerous and even lethal arrhythmias It is therefore understandable that most publications dealing with dangerous digitalis arrhythmias appeared when treatment with full doses was in vogue about forty years ago and again in recent years

Digitalis extrasystoles usually originate in the ventricles Reports of atrial extrasystoles caused by digitalis are scarce We have rarely seen them In all probability the reason for this rarity lies in the fact that the atria are under the influence of the increased inhibitory vagal tonus during digitalis therapy and this influence is lacking in the ventricles Experimentally the direct application of digitalis (or strophanthin) to the myocardium leads to atrial as well as to ventricular extrasystoles

Paroxysmal atrial tachycardias with partial A V block appear during the administration of

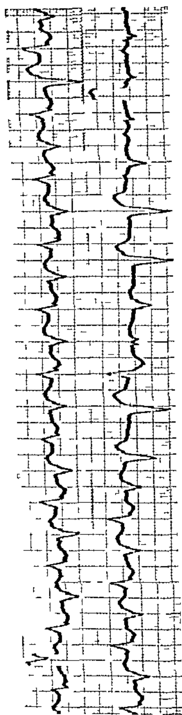


Fig 119 Ventricular tachycardia with alternating forms of the ventricular complexes in a patient with sinus rhythm The patient died suddenly presumably from ventricular fibrillation a few hours after the record had been registered

digitalis and disappear promptly after the exhibition of potassium chloride or acetate (figure 116)

The electrocardiogram usually permits the differentiation between digitalis extra systoles and the harmless ventricular extrasystoles that occur in the healthy The extrasystoles found so often in the healthy always originate in the same focus and show the same ventricular elec trocardiographic complex even if they persist for years Extrasystoles due to digitalis show a continuous variation of form since they originate in different foci and are due to an abnormal intraventric ular conduction (Scherf 1927) Extra systoles caused by organic heart disease (coronary sclerosis diphtheria) may also show varying forms of the ventricular complexes

This initiation of ectopic impulses by digitalis is a specific quality of the drug and is not caused by increased excitabil ity the latter is actually diminished

Figure 117 shows the electrocardio gram in the third lead of a patient with a rheumatic mitral lesion and extra systoles due to digitalis There is atrial fibrillation The first ventricular com plex conducted from the atrium in the tracing is followed by three multiform ventricular extrasystoles the second by one The third conducted complex is fol lowed by six extrasystoles and then by an abnormal automatic beat which is a characteristic digitalis effect

In figure 118 obtained from an other patient atrial fibrillation is also present (lead II) The first beat is fol lowed by three ventricular extrasystoles of different form The next beat after a pause is followed by a paroxysmal ventricular tachycardia with alternating form of the ventricular beats These

tachycardias precede the stage of ventricular fibrillation They are rarely seen except when digitalis is used in advanced myocardial damage They appear typically however if digitalis therapy is continued in cases of digitalis bigeminy

The important phenomenon of redigitalization is discussed in the next section

Elderly patients tend to show untoward effects after administration of moderate doses more often than younger individuals (fig 119)

Dosage

It is not advisable to follow a fixed scheme of treatment The digitalization of every new patient represents an experiment with an unknown outcome One can never know in advance how much digitalis a patient will need Only after it is determined how the patient responds to treatment how much digitalis is needed to obtain a desired effect and how long it takes until compensation is restored should an opinion about the prognosis of a decompensated case be offered

Full Dose Treatment As was previously mentioned and for the reason just cited the practice formerly in vogue and recently reintroduced of treating every decompensated cardiac patient for a certain number of days always with the same amount of digitalis is not correct It is just as improper to give schematically an amount of digitalis calculated according to body weight This is done by pharmacologists in animal experiments but is not permissible in the sick patient whose reaction to digitalis treatment is unpredictable

In recent years a similar method the full dose therapy was recommended Without regard to weight age or degree of failure the dose of 1 2 mg of digitoxin is given at one time Others recommended 1 7 or even 2 2 mg is the full dose The statement that 1 2 mg of digitoxin may be given at one time with complete safety (Gold et al) is certainly wrong as many publications show On the other hand Evans et al give 2 mg of digitoxin to one patient without even obtaining a slowing of the rate

Four facts speak against this procedure In the first place patients with the same type of heart lesion of the same age and the same body weight and even the same degree of decompensation may require entirely different amounts of digitalis Furthermore the wisdom of administering large doses to restore compensation as quickly as possible may be doubted Naturally one wishes to help as soon as possible and to improve the cardiac condition in an emergency Nevertheless the average cardiac patient who requires digitalis for rapid ventricular action caused by atrial fibrillation or for decompensation does not have to be digitalized within 24 hours The old mechanical conception of decompensation no longer suffices We have learned that most tissues and cells of the body live under abnormal conditions in a patient with congestive heart failure the advantage of changing the situation quickly is questionable Nothing is gained by restoring the circulation in these patients within a few hours instead of a few days indeed the disadvantages are great The third and most important reason for

not utilizing the "full dose" treatment was mentioned in the preceding pages when it was pointed out that the appearance of dangerous extrasystolic arrhythmias even after small doses of digitalis can never be foreseen. Finally, caution against the employment of large doses is required because focal necrosis appears in the myocardium in the experimental animal after the administration of sublethal doses of digitalis. While similar changes have not been observed in man even after the use of large therapeutic doses, one should not forget that injury to the tissue cells may occur despite the fact that such injury may not be demonstrable by our rather crude histologic methods.

Actually severe signs of intoxication have been seen, particularly in elderly patients, even after the administration of 0.6 mg. of digitoxin (Fremont and King). We have seen toxic prefibrillatory arrhythmias and atrial tachycardias after 0.3 mg. of digitoxin daily, and the lassitude and nausea may persist for weeks.

Not only does every species of animals have a different sensitivity to digitalis, but the sensitivity of different members of the same species of healthy laboratory animals varies. This is true much more for sick human beings who at different times need different doses.

Furthermore, a "half dose" in a patient with atrial fibrillation brings the rate down from 160 to 85, while the "full dose" brings the rate down from 160 to 75 in the same patient (Kay). The dangers of larger doses are infinitely greater. The benefit is small.

There is no "average" initial or maintenance dose except that which is calculated on paper. Therapy is highly individual. Therefore, the recent revival of the "full digitalizing dose," assuming that the amount needed by every individual is the same independent of weight, age, etc., cannot be accepted.

Initial Dosage. While treatment with excessively large doses of digitalis given within a short time should be avoided, the administration of moderate doses proportionate to the severity of the decompensation is proper.

One tenth of 1 Gm. of the standardized (assayed) powdered leaves in the form of tablets will be considered as a standard unit. Even here the strength may change. Thus, the assayed digitalis of USP XI was much stronger than that of USP X, while the digitalis of USP XII was again slightly weaker.

The dose given to a patient with mild decompensation who does not present severe manifestations of congestion may amount to 0.15—0.2 Gm. a day of assayed digitalis in the form of powdered leaves or tablets. In more severe cases of decompensation the daily dose is increased to 0.1 Gm. three or four times daily.

Only those subjects who are known to require much larger doses of digitalis than the average patient should receive about 0.6 Gm. of digitalis daily. This group comprises patients with hyperthyroidism, fever, or pulmonary embolism. The literature on the question of the greater resistance to digitalis of patients belonging to one of these groups is large and somewhat contradictory. It seems established, however, that slowing the heart in patients with hyperthyroidism combined with atrial fibrillation is difficult. Why a larger amount of digita needed by virtue of the presence of fever is not yet decided. Another une

difficulty in obtaining the desired slowing of the heart in atrial fibrillation is encountered in patients with pulmonaray embolism This complication should always be suspected if — in the absence of fever or hyperthyroidism — the expected effect of digitalis is not obtained

Large doses of digitalis are given only as long as evidence of severe decompensation persists As soon as improvement appears treatment is continued with smaller doses

One can never predict the duration of digitalis therapy Many days or even weeks may elapse before it appears that the best possible result has been obtained or until digitalis vomiting or bigeminy prevents further administration of the drug Long duration of the period of digitalis medication in itself is no contraindication for continuation of the treatment

Maintenance Treatment If digitalis therapy in a decompensated lesion or myocardial disease is carried to the point where the patient seems fully compensated and all signs of congestion have disappeared or when this result is impossible if the optimal state seems to exist the administration of digitalis should not be discontinued to be resumed only when the manifestations of decompensation reappear It is also improper to recommend a certain amount of digitalis purely schematically for a number of days each month for all patients It is better practice with most patients not to pause entirely in the administration of the drug an adequate amount should be given to maintain the patient in the best condition attainable by treatment

In cases of atrial fibrillation in which digitalis is given only to keep the ventricular rate low the rate itself is the best guide for the dosage These cases in particular require maintenance treatment Patients who develop decompensation following an acute infection or excessive physical effort may not require maintenance treatment Full compensation may be preserved if the cause for the decompensation has vanished

The dose for maintenance treatment should also vary according to the needs of the patient If compensation was readily restored and if this was achieved with relatively small doses of digitalis 0 1 Gm digitalis given once on every day or on every second day may suffice If larger doses were originally required for a long period the maintenance doses also will usually be larger One will find that some patients may need 0 2 or even 0 3 Gm of digitalis every day because even a temporary and slight reduction of the dose causes the reappearance of signs of decompensation Naturally the amount of digitalis required by the individual patient will not always be found instantly after some observation the doses may have to be increased or decreased Likewise the unavoidable alteration of the sensitivity of the patient changes of the heart and also changes of the strength of the drug may force a change of dosage Digitalis made by different manufacturers which were assayed cause quite different responses in man at different times and in addition the absorption and stability of different preparations varies

For these reasons patients who require maintenance treatment with digitalis need periodic re examination by their physicians By the continuous adminis

tration of digitalis patients avoid the frequent change from compensation to decompensation and within certain limits they may be kept active for years There is no danger of acquiring tolerance for digitalis from prolonged administration the drug always remains effective

If some untoward sign mentioned in a previous chapter including digitalis extrasystoles appears and one finds that continued treatment is necessary merely diminishing the dose often will suffice If the patient does not tolerate even the smallest doses without exhibiting side effects one may be compelled to stop the drug completely and try again after a short period during which other cardiac stimulants such as caffeine or theophylline are given

Different Preparations of Digitalis

In selecting a preparation it should be remembered that the galenic forms of digitalis are still among the most reliable provided the assayed drug is employed

The powdered leaf or the tablet made from powdered leaves are most commonly used Formerly digitalis tincture was used widely if fresh it is very satisfactory It is rarely prescribed at present and perhaps should be avoided because it must be fresh and reliable in order to give good results The deterioration of tablets or powdered leaves by storage is negligible

The number of special digitalis preparations on the market is legion and new ones constantly appear Most of these preparations are satisfactory Few have any advantage in comparison to assayed digitalis tablets If a new preparation is tried the physician should familiarize himself with the correct dosage which is frequently at variance with the manufacturer s recommendation Only experience gained by the use of the preparation in many patients will show its value It is unwise for the physician to change continually to new and different preparations and to adopt at once those which are highly eulogized Certain advantages are claimed for every new preparation of digitalis Many of these attributes to be sure are based on experimental investigations on the frog or cat heart and have little value at the bedside If it is asserted that a preparation is nontoxic does not cumulate and does not produce vomiting it should not be employed it is inert A good preparation of digitalis is toxic does cumulate at least to a slight degree and must cause vomiting when it is administered in sufficiently large doses

Preparations of digitalis made from the whole drug (Digifortis Digalen Digilanid Digifolin and many others) contain a mixture of glycosides and possess no advantage over the standardized preparations they are rarely used in the United States today They may be used where the standardized powder or tablets are unobtainable The physician is advised to employ only one or two of these preparations in order to obtain some experience Even the strength of these special preparations may change for various reasons and a physician who does not thoroughly know the digitalis employed may become aware of this change too late It is a great handicap to work with two unknowns the preparation of digitalis *and* the patient

Most good commercial preparations are assayed One should not rely however too strongly upon the statement of the manufacturer for dosage The amount should be determined on the basis of personal experience If the directions printed on packages are followed the dose prescribed frequently is too small

Every physician should be acquainted with the action of a few special preparations of digitalis Some are very powerful Since some are obtainable in the purified crystalline state the dosage is exact and the biologic assay with all its difficulties is unnecessary

The oldest pure crystalline digitalis glycoside is digitoxin (digitaline Nativelle) It is quantitatively absorbed when given orally The different preparations of digitoxin are not of equal purity and not of equal strength A dose of 0 1 mg given three times daily is as active as three tablets of 0 1 Gm powdered leaves given daily Only for special purposes e g to transform atrial flutter into fibrillation should larger doses be given and then only under close supervision Nausea and vomiting soon appear with large doses Digitoxin is fixed to the albumin fraction in the blood and disappears completely from the blood only after 24 hours It is therefore not one of the rapidly acting glycosides Only 7 per cent of the glycoside is dissipated daily in the heart muscle Therefore digitoxin is a glycoside with a great tendency to cumulate For the restoration of compensation in patients with coronary sclerosis or following a myocardial infarction preparations of digitoxin are very useful In many patients the prolonged administration of 0 2 mg daily is necessary to preserve compensation In others particularly in elderly people this dose is too large and causes toxic phenomena to appear Some patients need 0 1 mg every other day or even smaller amounts

A very satisfactory glycoside isolated from digitalis lanata is the crystallized digoxin (Smith) It can be given by mouth or by injection Following an intravenous injection ventricular slowing begins in five to ten minutes and the maximum effect is attained within an hour After oral administration improvement begins within an hour and may be pronounced within six to seven hours Tablets contain 0 25 mg of digoxin and the material for injection contains 0 5 mg per ml

The third crystalline glycoside also isolated from digitalis lanata is Cedilanid (lanatosid C) The components originally isolated (digilanides) were found to cumulate less than digitoxin Ampules and tablets are available One ml of the liquid contains 0 2 mg of Cedilanid The first dose is usually 2—4 ml It may be repeated on the next day according to the condition of the patient

Lanatosid C is bound but little to blood proteins and acts quickly almost like strophanthin It is rapidly eliminated

Acetyl digitoxin is also derived from the digitalis lanata It is obtained from lanatosid A fraction by enzymatic cleavage of 1 molecule of glucose It is absorbed rapidly Therefore it is recommended particularly for paroxysmal tachycardias and fibrillation (Loeffler et al)

Citalin a mixture of amorphous digitalis glycosides that has been employed on the European continent for many years recently has been reintroduced (Batter

man) We employed it for many years as Verodigen and found it reliable However the claim that gitalin (amorphous) helps when other glycosides fail is unjustified

Method of Administration

In the majority of cases digitalis is given by mouth in the form of the assayed powder tablets drops or pills of one of the reliable commercial preparations In exceptional cases in which more rapid effects seem necessary digitalis is given intravenously using a crystallized pure glycoside (digitoxin digoxin cedilanid)

The rectal suppository represents another method of administration but it is rarely used in this country By rectal administration of purified digitalis gastric irritation due to ballast substances and saponins is avoided Furthermore the drug is absorbed by the mucosa and conducted by the hemorrhoidal veins into the inferior vena cava without retention in the liver The rectal administration of digitalis has the same effect as a slow intravenous infusion The amount of digitalis which should be given by rectum is the same as that which would be given by mouth

It is easy to administer the whole dose of digitalis for the day in the form of two suppositories in this way one obtains better absorption without gastric irritation Particularly in those patients who present evidence of marked hepatic congestion or who for some reason are unable to receive injections of a crystalline digitalis glycoside or strophanthin suppositories are useful

One of the best is the digilanid suppository If a dose or a preparation different than that obtainable from the manufacturer is desired the suppositories can be prepared by any pharmacist by mixing the corresponding amount of a purified digitalis preparation (digitaline digalen digilanid) with cacao butter Usually it is possible to mix about 15 drops of an appropriate digitalis solution in the amount of cacao butter required for one suppository

Another advantage of a suppository is the possibility of admixing other substances which must be administered by rectum Thus patients with Cheyne Stokes breathing may need aminophylline in addition and if necessary an hypnotic may be added For example

Digalen	0 5 ml
Aminophylline (Theophylline ethylendiamine)	0 5 Gm
Ol Cacao q s f suppos	

One suppository may be given in the morning and sodium phenobarbital may be added to another which may be administered in the evening

It is not advisable to administer digitalis intramuscularly since local pain invariably follows and the temperature rises indicating muscular necrosis

Preparations with Digitalis Like Action

There is a large number of so called digitalis preparations of the second order they are powerful and active drugs Most of these preparations have effects similar to those of digitalis but rarely do they accomplish more than digitalis In the rare case of idiosyncrasy to digitalis such agents may be em

ployed we find them useful on patients who are under the impression that the administration of digitalis means the beginning of the end

Squill is perhaps the best known representative of this group It is at the same time one of the oldest known drugs being mentioned in the Ebers papyrus From the drug a pure crystallized glycoside, Scillaren A has been isolated (Stoll) and its activity can be compared with good preparations of digitalis The single dose of Scillaren by mouth is 0 8 mg the suppositories contain 1 mg of the glycoside The side effects if these drugs are employed are the same as those of digitalis including ventricular extrasystoles

Among the other drugs of this group (Adonis vernalis Nerium Antiaris Convallaria majalis) only Helleborus deserves mention Its purified extracts proved very active in its pharmacologic characteristics it stands midway between digitalis and strophanthin (Scherf)

STROPHANTHIN

Closely allied to the digitalis glycosides although different in many respects are the glycosides of strophanthus Of the many compounds in this group only three are used clinically

Preparations

K Strophanthin Strophanthin kombè or k strophanthin is an amorphous powder In recent years it has been possible to isolate a crystalline glycoside from k strophanthin which represents about three quarters of the amorphous glycoside It is called strophoside K strophanthin is mentioned in the United States and in the British Pharmacopoiea and it was widely used in Germany under the leadership of Fraenkel

G Strophanthin Strophanthin gratus or g strophanthin was isolated as a more stable crystalline product by Arnaud (1888) and is called by its African name ouabain This preparation is widely used in French medicine

Acetyl strophantidine an aglucone is a synthetic preparation prepared from the seeds of strophanthus kombe It works more rapidly than any other preparation and therein lies its danger Toxic rhythms are common and in our opinion there is no place for the use of this compound in clinical medicine

Pharmacologic Effects

The action and side effects of strophanthins on the heart muscle particularly on systole and on the blood vessels are identical to those of digitalis Some of the differences are their great solubility in water the small amount of fixation of strophanthin in the heart and — in connection with this — the slight cumulation If a dose of digitoxin is given 93 per cent of the drug is still present in the heart after 24 hours and 50 per cent after 9 days Of a dose of lanatoside C after 24 hours only 80 per cent is present and only 64 per cent after 48 hours Of strophanthin only 50 per cent of its action is present after one day and only

one eighth after three days (Rothlin and Bircher) The most important difference from a clinical standpoint has been the almost immediate action of strophanthin This is advantageous when it is necessary to improve a severe decompensation rapidly With the pure crystalline glycosides of digitalis purpurea (digitoxin) and digitalis lanata (digoxin cedilanid) which may be given intravenously only slightly less rapid action (30—60 minutes) is obtainable

There are few potent drugs about which opinions are as divided as strophanthin (Kisch) While in some countries particularly on the European continent strophanthin is employed in practically all types of decompensation much more often than digitalis and in many large institutions seems to be the drug of choice in other countries strophanthin is scarcely known

Several facts account for this difference of opinion First overenthusiastic physicians stressed the digitalis like effect of strophanthin and went so far as to use it as a synonym for digitalis neglecting however to stress the important and essential differences between the two Second the doses recommended (even in recent times) were much too large led to untoward effects and discouraged the physician from further use Third most preparations of strophanthin are quickly destroyed particularly by the alkaline glass of the ampules and lose their potency within a short time Therefore many preparations now dispensed are disappointingly weak unless certain types of glass are used for the containers If injection of the inactive contents of these ampules a few times in emergencies elicits no effect the disappointed physician doubts the reports of other observers and decides to use only digitalis in the future

The ampules of ouabain at present are the best preparation of strophanthin obtainable in this country

Indications

In general strophanthin is indicated in the same conditions as digitalis Since these preparations are active only if given by injection there is the disadvantage of greater expense to the patient for he is forced to have an injection daily or almost daily for some time accordingly we feel that for routine treatment digitalis is by far preferable and that strophanthin should be given only on definite indications

Formerly the fact that its exact dosage could be prescribed without the necessity of bioassay was of great advantage but such procedure is also possible now with the crystalline preparations of digitalis

Strophanthin is indicated in an acute emergency If for example in an untreated or inadequately treated pregnant woman with mitral stenosis acute heart failure appears during childbirth or if a protracted and severe pulmonary edema appears in a patient with hypertension and does not react well to symptomatic therapy or if a patient is admitted to the hospital with a surgical emergency requiring immediate operation and atrial fibrillation with a very rapid ventricular rate is found the administration of strophanthin will usually bring noticeable improvement within a few minutes However it must be stressed

is present due to pulmonary congestion In these cases rapid dehydration may furnish quick relief In the majority of cases however treatment with diuretics is initiated only after the circulation has been improved somewhat by digitalis Often even the strongest diuretics evoke only a slight response when given to congested and decompensated patients If diuretic treatment is delayed a few days until the circulation is improved somewhat by digitalis striking effects may be obtained with much smaller amounts of diuretics Often the diuretics even become superfluous because rest in bed diet and digitalis alone cause a profuse diuresis

The diuretics *which are the most effective and if properly employed* distress the patient least by unpleasant untoward actions particularly on the gastrointestinal tract are certain organic preparations of mercury Since their use is not permissible in some cases every physician should be acquainted with the xanthine derivatives and other diuretics as well The action and the method of administration of the latter preparations will be considered first

Xanthine Derivatives

Xanthine preparations (purine bodies) have caffeine theobromine and theophylline as chief representatives While caffeine exerts its strongest effect as a stimulant of the central nervous system theobromine and theophylline are pronounced diuretic agents They also dilate the coronary arteries

All these preparations increase water and sodium chloride diuresis This effect seems to be accomplished by a direct action on the kidney Diminished tubular absorption has been assumed partly it is due to improved contractility of the heart and to mobilization of water and salt in the tissues Vasodilatation and better perfusion of the kidney originally held responsible seem to play a minor role All these drugs also stimulate the heart Thus theophylline increases the output of the damaged heart of the dog in the Starling preparation This effect is independent of changes of the coronary blood flow

Caffeine is rarely used as a diuretic since its stimulating action on the central nervous system is so pronounced that it leads to unpleasant sensations

The xanthine preparations most commonly used as diuretics are theobromine and its salts or *theophylline with various combinations*

The customary method of administering moderate doses of xanthine bodies distributed throughout the day often produced little diuretic action It is better not to scatter the doses rather large amounts should be used at short intervals and only for a short time

If the diuretic effect of one of these drugs ceases there is no justification for continuing the remedy with larger doses It is better to prescribe another preparation which may act excellently although it may be closely related to that which was originally given

Pure Theobromine In using pure theobromine we observed the best effect when it was given in [illegible] after lunch and if the same dose was repeated

two and four hours later thus a total of 3 Gm are given in divided doses in the afternoon If patients become too stimulated by the drug and sleep is disturbed theobromine may be administered after breakfast and two as well as four hours later

Theobromine Calcium Salicylate This drug known under the name Theocalcin is said to cause less gastrointestinal disturbance but we found no difference in comparison to some of the other purine bodies The dose is 3 Gm daily

Theophylline The strongest diuretic effect is obtained with pure theophylline It is best to administer it in enteric coated tablets similar tablets are also available for some of the other xanthine preparations The diuretic effect of theophyllinum purum is much stronger than that of theophylline with ethylendiamine (aminophyllin euphylline) or theophylline with sodium acetate The rule of giving large doses within a relatively short time is particularly applicable with this preparation The best diuretic effect is obtained if 0 3 Gm is given after meals three times a day but only on every fourth day Such jolts of theophylline are greatly superior to small doses daily The 24 hour diuresis may amount to 5 liters Sometimes pure theophylline given in this way may be effective when mercurial diuretics fail (Faltitschek and Scherf)

If the preparation is used in the same dosage daily its diuretic effect often ceases completely within a few days If administered only on every fourth day as is the case with the mercurial diuretics it remains active for an indefinite period

Vogl recommends 0 5 Gm of aminophyllin injected intravenously twice daily very slowly for the purpose of diuresis

Untoward Effects Whenever xanthine preparations are administered it is well to inform the patient that untoward effects may occur In the event that such phenomena appear the patient is not taken by surprise and is not alarmed Moreover he is informed in advance that discontinuance of the remedy will afford rapid relief If the patient is unacquainted with the possibility of unpleasant untoward reactions the appearance of nausea vomiting severe headache and restlessness with increased excitability may be alarming All these phenomena are more common with theophylline than with other xanthines To counteract the central stimulating effect the administration of phenobarbital (0 03—0 05 Gm) with each dose of theophylline is recommended

A rare but nevertheless important contraindication to theophylline is epilepsy The preparation stimulates the cerebral cortex and may lead to attacks in epileptic individuals This effect as well as headache and hyperirritability are also prevented or diminished by the addition of phenobarbital to each dose of theophylline

Antidiuretic Action of Sedatives Analgesics and Hypnotics

Phenobarbital in the doses mentioned does not depress the diuretic action of theophylline Larger doses however as well as moderate doses of morphine or aminopyrine may not only abolish the effect of diuretics but may also inhibit normal diuresis to a high degree

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The administration of potassium salts as diuretics has been revived in recent years Potassium chloride or acetate are recommended Doses of about 5 Gm daily seem to be optimal Potassium chloride is obtainable in enteric coated tablets Occasionally nausea occurs during the administration of the drug and methemoglobinemia has followed the use of potassium nitrate If large doses are used or if kidney function is impaired the level of blood potassium increases The acid base balance is changed in some patients toward the acid side

Mercurial Diuretics

Type of Preparations Some inorganic mercurial preparations e g calomel have been used for many years as diuretics The action of calomel however was unreliable and intoxications were frequent The discovery of the diuretic action of organic soluble salts of mercury in 1920 was one of the greatest advances in the treatment of cardiac patients in recent years The duration of life in many patients is prolonged for years and countless others are enabled to lead an active life with the employment of these drugs The discovery was quite accidental Novasurol (Merbaphen) was used for about three years in the treatment of syphilis until its diuretic action was observed in a case of syphilitic aortitis (Saxl and Heilig Vogl) Later Salygran (mersalyl) and novurit (Mercupurine Mercurin) were introduced as well as neptal esidrone Mercuhydrin Thiomerin and others It is often claimed that the first preparation Novasurol (Merbaphen) was more toxic than the others but it seems that as experience increased the preparations were used more cautiously and therefore toxic manifestations became rare These diuretics contain about 40 mg of mercury per ml

Since the introduction of Mercupurine (novurit) which contains a very small amount of theophylline it has been claimed that this addition considerably enhances the diuretic effect of the mercurial salts Therefore theophylline was also added to most of the other preparations It is claimed that the addition of theophylline makes the mercurial diuretic less toxic and that they are less irritating locally when injected intramuscularly At bedside in appropriate cases by alternating the use of mercurial diuretics with and without theophylline we were unable to discover an appreciable difference

Fundamentally the diuretic action of all above named mercurial preparations is equal It has been claimed however that some such as neptal and esidrone are slightly more toxic than the others Mercupurine seems to act a little sooner and diuresis follows the injection more rapidly But the end result is the same as with the other diuretics The remarks which follow are equally applicable for all preparations including Mercuhydrin and Thiomerin which is a mercaptan compound and which can be given subcutaneously

Pharmacology The preparations lead to a marked water diuresis and to a relative and absolute increase of the sodium chloride diuresis More than 40 Gm of sodium chloride may be excreted in 24 hours In a boy of 15 years 1 ml of neptal caused a diuresis of 14 430 ml of urine in 24 hours 570 ml of urine were

in the urine of patients with congestive heart failure is increased The presence of a concentrated dark urine (after exposure to air for a few hours) due to urobilin shows that it is safe to use mercurial diuretics

The presence of colitis in any form constitutes another contraindication to mercurials Colitis is one of the most dangerous manifestations of mercury intoxication and therefore the administration of these compounds should be avoided when colitis is already present It is also unwise to give purgatives which irritate the large intestine on the days of the injection of mercurial diuretics Decayed neglected teeth and the presence of a profound anemia or cachexia are further contraindications since mercurial diuretics have a relatively high content of mercury and therefore act as cell poisons

Untoward Effects Mercurial diuretics may cause untoward effects by different mechanisms those of mercury intoxication those due to hypersensitivity or those caused by a too marked loss of water and electrolytes

MERCURIALISM The earliest indications of mercury intoxication are metallic taste salivation gingivitis stomatitis and colitis The latter is often hemorrhagic in character The patient may collapse so suddenly that no melena occurs All these manifestations of mercurial intoxication were rare since the preparations were used with proper caution and in appropriate cases Unfortunately it has been recommended recently that mercurial diuretics be given in intervals that prove to be too short with the result that evidence of intoxication is observed more often Agranulocytosis may occur

To counteract the effect of mercury BAL (5 mg per Kg) is given intravenously every 4 hours

HYPERSENSITIVITY Hypersensitivity to the mercury ion may exist but more often it is connected with the specific organic compound used Therefore change of the preparations often helps to avoid further abnormal reactions Dizziness fall of blood pressure drowsiness and headaches urticaria and erythematous dermatitis may appear fever collapse and cyanosis with death in a few minutes have been observed Dyspnea and attacks of asthma have followed even the first injection There is experimental and clinical evidence that ventricular extrasystoles paroxysmal tachycardias and ventricular fibrillation may appear owing to the direct effect of the mercury ion on the heart muscle These effects particularly the cardiac arrhythmias appear for the most part after intravenous injections

CONSEQUENCES OF DIURESIS The loss of water sodium and chloride causes somnolence cramps in the calf muscles and sometimes delirium or mental confusion Profound weakness may appear due to loss of potassium Therefore fruit juices should be ordered These complaints were known to follow a profuse diuresis long before the mercurial diuretics were introduced Since the excretion of sodium and chlorides need not parallel the water diuresis occasionally one observes these phenomena after moderate diuresis but may miss them after an unusually profuse one

The loss of calcium ions may lead to tetany Acute gout has appeared in a series of patients who had had previous attacks of gout A disturbance of electrolyte balance may be responsible

It has been claimed that the influx of fluid from the tissues increases the coagulability of the blood and therefore increases the danger of thrombosis and embolism

Fever and cutaneous manifestations (rash) may develop after an injection The fever may reach 39 C but rarely lasts longer than 24 hours the simultaneous use of calcium gluconate may help avoid these complications

However the intravenous injection of calcium preparations is dangerous especially in digitalized patients In one personally observed case it was followed by ventricular fibrillation in another patient who had not received digitalis before a long and dangerous ventricular standstill instantaneously followed the injection Intramuscular injections of calcium salts are free from these dangers

The appearance of abnormal reactions cannot be predicted They have been observed in patients who responded normally to preceding injections If however an abnormal reaction occurs once it is unwise to employ the intravenous route Sudden lethal accidents are not observed after intramuscular injections of mercury

While collapse or even sudden death immediately following an injection due to allergy undoubtedly occurs such catastrophes are rare and should not militate against use of these excellent agents Several series of more than 8000 injections have been reported without the occurrence of any untoward effect

The profuse diuresis may lead to an acute urinary retention in elderly patients with prostatic hypertrophy

Two other side effects of therapy with mercurial diuretics merit attention

(1) THE LOW SALT SYNDROME This develops in patients who receive mercurial diuretics too often while on a salt free diet or when losing much salt from the kidney The diuresis in these patients stops and they gain in weight they have low plasma levels of sodium (from 140 to 120 mEq per liter or less) and chlorides (from 100 to 86 mEq per liter or less) drowsiness and weakness may appear simultaneously Nausea and vomiting may occur and abdominal cramps are common There is a low carbon dioxide combining power and the urea as well as the NPN are increased often to values over 100 This acidosis and azotemia are rarely relieved by the infusion of hypertonic saline solutions (200—300 ml of a 5 per cent sodium chloride solution) since irreversible intracellular changes appear The outcome is usually fatal The syndrome occasionally appears in cardiacs without ascertainable reason (movement of electrolytes? abnormal water retention? action of aldosterone?)

(2) HYPOCHLOREMIC ALKALOSIS (low chloride syndrome) The excretion of chloride under the influence of an injection of mercury is excessive and may be greater than that of sodium When the chlorides fall below 86 mEq per liter no diuresis results from the injection A fall by only 4—6 mEq may be of

Ammonium chloride is necessary only if mercury alone does not suffice or if injections of mercury are repeated at short intervals and the danger of hypochloremia exists

If doses not larger than 2 ml are given intramuscularly at intervals of no less than four days no accident will be seen in the course of many thousands of injections apart from hypersensitivity Certainly the injections must be discontinued at once with evidence of colon irritation or stomatitis It is astonishing how well the injections are tolerated One of our patients received more than 700 injections in 14 years Such patients are often observed and receive their injections on every *fourth* or *fifth* day without any sign of renal irritation

The combination of a mercurial diuretic with decholin (5 ml) in the same syringe injected very slowly has been frequently recommended However unpleasant accidents caused by decholin have been observed

No examination gives us as clear a picture of the effect of our diuretic therapy as weighing the patient

Mode of Administration The customary method of administering mercurial diuretics was for many years by intravenous injection The injection must be properly performed Some patients are so sensitive that the small amount of the preparation on the needle to say nothing of a paravenous injection suffices to cause a severe necrosis of the skin that requires months to heal For this reason the needle through which the preparation is withdrawn from the ampule is never employed for the injection The preparations are injected only if one is absolutely sure that the injection is exclusively intravenous

Intramuscular injections are now the method of choice since dangerous hypersensitivity reactions can thus be avoided they usually do not hurt or are only slightly painful The original mercurial organic diuretic novasurol it may be recalled was for years given only intramuscularly none dared to essay intravenous injection Painful infiltration following intramuscular injection is avoided if 1 ml of a 1 per cent solution of procaine (or a similar preparation) is added to the mercurial preparation in the same syringe The addition of procaine not only prevents any immediate (though slight) pain but it prevents secondary inflammation and irritation (Freud and Meyer) The best site for the injection is located in the posterior axillary line three fingers below the crest of the ileum In obese patients the injection must be made with a needle of sufficient length if this precaution is not taken the injection may actually be subcutaneous or be made into the deep adipose tissue where it causes necrosis A true intramuscular injection never causes necrosis

All injections should be given early in the morning The diuresis follows the injection in two to three hours and for the most part is over by bedtime If the injection is given later during the day the night rest is disturbed The injection of mercurial diuretics into a pleural effusion or into ascitic fluid is dangerous and may lead to serious local irritation Marked diuresis may follow such injections but they possess no advantage The appearance of a profuse diuresis following an intra

peritoneal injection (done only in the presence of ascites) begins within a few hours and rarely exceeds two days This proves that ascitic fluid is quickly absorbed and reformed otherwise the rapid action of the injection would be incomprehensible

Suppositories of mercupurin or those made from some other organic mercurial diuretic produce a considerable diuretic effect (Dennig and Krause) They should be inserted after a cleansing enema The suppository should be covered with pantocaine or nupercaine ointment Fissures and hemorrhoids are a contraindication Since some suppositories contain a rather large amount of the active ingredient they should not be given more often than every four days Many times the suppositories cause diuresis only after preliminary preparation with ammonium chloride When the administration of injections is impossible for some reason suppositories may be tried

The oral administration of the organic mercurial diuretics was tried early (Saxl) and has been recommended repeatedly If 2 to 3 tablets are given daily some diuresis may be obtained Often evidence of intoxication develops and in one series of 39 cases toxic effects appeared in 14 This also holds for preparations introduced recently and declared nontoxic Orally administered mercury is often excreted days after its ingestion and cumulative effects are common

Ammonium chloride nitrate and sulfate if given in sufficient doses may alone provoke a moderate diuresis and increase the diuretic effect of the mercurials In the body the ammonium ions are synthetized to urea and the acid radical remains Ammonium chloride is preferred because methemoglobinemia has followed the employment of ammonium nitrate The mode of action is not entirely clear Presumably acidification may help to liberate mercury in the renal tubuli The administration of an acidifying diet also increases the water and sodium chloride diuresis caused by theocin (theophylline) A similar purpose is served by the administration of 20 ml of dilute hydrochloric acid in 500 ml of water

Large doses of ammonium chloride are recommended We advise 6 Gm ammonium chloride in enteric coated tablets (i e 6 tablets of 1 0 Gm) daily for two days before and 3 Gm on the day the injection is given Others suggest smaller doses for instance 2 Gm of ammonium chloride two hours before the mercurial diuretic is injected Untoward effects (gastric irritation) are rare with enteric coated tablets In many cases ammonium chloride is unnecessary since the mercurial injection alone affords a satisfactory result There is no justification for administering ammonium chloride daily for a long time prescribed in this manner it loses its diuretic action and causes acidosis

Diomax — Diuril

A mild diuretic effect of sulfonamides has been known for a long time and one synthetic preparation Diomax with a new organic structure (acetazole amide) has a marked diuretic action with very few side effects

Ammonium chloride is necessary *only if* mercury alone does not suffice or if injections of mercury are repeated at short intervals and the danger of hypochloremia exists

If doses not larger than 2 ml are *given* intramuscularly at intervals of no less than four days *no accident* will be seen in the course of many thousands of injections apart *from* hypersensitivity Certainly the injections must be discontinued *at once* with evidence *of colon* irritation or stomatitis It is astonishing how well the *injections* are tolerated One of our patients received more than 700 *injections* in 14 years Such patients are often observed and receive their *injections* on every fourth or *fifth day* without any sign of renal irritation

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the hydrogen cycle and 20 per cent in the potassium cycle Finally Katonium up to 75per cent an ammonium and 25per cent a potassium resin is given in doses of 15 grams three times daily

The resins also seem to absorb riboflavin and thiamin Since the absorption of potassium may lead to a dangerous hypokalemia one third of the resin is in the potassium cycle so that potassium ions are available for reabsorption Intake of resins can also cause hyperchloremic acidosis because hydrogen ions are released and basic ions lost in the feces chlorides are not removed by the usual resins Therefore a large percentage of the resins are in the ammonium cycle and are able to release the ammonium in the gastrointestinal tract

In vitro 1 gram of resin removes approximately 10 mEq of sodium but in vivo the amount depends upon the intake of sodium and on other factors

The acidosis is partly compensated by ammonia formation and the excretion of more carbon dioxide via the lungs The acid urine may cause albuminuria and casts to appear

While resins can be prescribed with reasonable safety they should never be administered in the home continuous control of the sodium chloride potassium blood levels as well as of NPN and carbon dioxide combining power are needed With the increase of chloride in the blood and a decrease of bicarbonate plasma concentration there is great danger of a high NPN Prolonged administration resulting in the removal of calcium may lead to bone demineralization With removal of potassium digitalis toxicity appears in patients taking this drug and dangerous arrhythmias occur Rarely fecal impaction occurs

Whenever loss of appetite weakness or vomiting appear therapy should be discontinued and one should check the blood for the substances mentioned above

The granulated resins are best taken with cream as in a cereal the powdered forms with orange or other fruit juices which also serve to supply potassium.

The indications are few While diet may be more liberal and may contain more salt few people like the resins which taste like sand and which they must ingest only in order to get more of the food they desire In patients who are sensitive to mercury that is to all mercurial diuretics the resins may save or prolong life It should be stressed however that even if resins are taken the diet can never be really liberal

Renal damage is an absolute contraindication Many refuse the resins because of diarrhea or constipation vomiting nausea or loss of appetite

Southey Tubes

When all diuretics fail and tense edema is present drainage with Southey tubes is necessary This represents a last resort since the danger of secondary infection and the development of erysipelas is great Fortunately this procedure has rarely been necessary since the introduction of the mercurial diuretics But there are times when tubes must be employed because all other therapy is fruitless

We have seen patients who responded to ordinary diuretics well only after the successful employment of the Southey tubes and then were kept free from edema for years

TREATMENT OF CHEYNE STOKES RESPIRATION

Cheyne Stokes breathing and the various forms of paroxysmal nocturnal dyspnea which result from cardiac failure (left ventricular failure) represent indications for digitalis therapy However some time elapses before digitalis helps unless the rapidly acting pure glycosides or strophanthin are given Furthermore not every patient is relieved by digitalis and signs of failure may persist despite energetic digitalization Therefore it is often necessary to treat Cheyne Stokes respiration symptomatically

Oxygen Since an oxygen deficit and hyposensitivity of the centers have long been recognized as precipitating causes of Cheyne Stokes breathing frequently an effort has been made to obtain improvement by means of oxygen inhalation as well as by agents which stimulate the cerebral centers

As a matter of fact the inhalation of oxygen acts immediately and abolishes Cheyne Stokes in most cases only a few patients do not respond The apneic pauses vanish and respiration becomes regular Naturally improvement persists only as long as the administration of oxygen is continued

Inhalation of oxygen by nasal catheters is useful and may tide the patient over distressing periods The great anxiety and restlessness of the patient with a severe form of Cheyne Stokes often interferes with their use and makes the employment of oxygen masks also impossible The oxygen tent is superior and may quickly abolish periodic breathing as well as the mental confusion and restlessness combined with it

Central Stimulants All attempts to influence Cheyne Stokes respiration by the administration of central nervous system stimulants have failed Lobeline strychnine atropine and coramine as well as caffeine are useless for this purpose

Aminophylline (Theophylline with ethylenediamine) which is also known as metaphylline euphylline has an almost specific action This compound was used for many years as a diuretic and vasodilator while its excellent effect on patients with Cheyne Stokes breathing was only occasionally mentioned until this action was stressed by Vogl The relief afforded by the preparation is so great that the term miraculous is often used by patients and even by the physician in charge

A few minutes following the injection the periodic alternation of dyspnea and apnea disappears and the respiration becomes regular With this the restlessness and anxiety subside and patients who have not had a good night for weeks sleep quietly It acts like magic The patient is not compelled to sit up nor to pace the room restlessly but lies quietly in bed seeming and feeling altogether like a different person

The most effective method of administering the preparation in patients with Cheyne Stokes is the intravenous injection An ampoule containing 0 24 Gm of aminophylline is injected very slowly A rapid injection leads to marked va o

dilatation and flushing with the sensation of warmth not unlike the sensation following an intravenous injection of a calcium or quinine preparation In the patient suffering from a cardiovascular disorder too rapid an injection may be followed by vertigo marked fall of blood pressure and even a mild collapse Therefore the aminophylline should be diluted with saline or a 5 per cent solution of glucose and injected so slowly that the injection requires at least 5 minutes If this method is followed no harm need be feared It is best to give the injection during the evening since Cheyne Stokes respiration tends to occur or to become worse at night If necessary an injection can be given twice in 24 hours Hyper sensitivity to aminophylline (headache vomiting) is rare This treatment may be continued for a long time the mere fact that the preparation is employed over a considerable period is in itself no reason for stopping it

Intramuscular injections are not recommended because they often cause pain Occasionally however an intramuscular injection is well tolerated perhap due to a better balance of the hydrogen ion concentration The dose for intramuscular injections may be the same or a double amount (0 48 Gm) Almost as effective as an intravenous injection is a retention enema An ampoule containing 0 48 Gm or a corresponding amount of aminophylline powder (0 5 Gm) is diluted with about 30 ml of tap water and given as a retention enema Similar but a little less effective is the administration of aminophylline in a suppository containing 0 5 Gm The administration of aminophylline as a suppository results in satisfactory levels of theophylline in the blood plasma (Glass et al) One suppository is given at bed time and another during the day if necessary Aminophylline tablets have little value in Cheyne Stokes breathing

The mode of action of aminophylline is still obscure Aminophylline is a vasodilator but this effect is hardly responsible for the improvement since stronger vasodilators like the nitrites and even large doses of nitroglycerin are not effective in Cheyne Stokes respiration Theophylline like all xanthine bodies is a central stimulant But other central stimulants even though stronger like caffeine do not influence Cheyne Stokes breathing We are dealing therefore with a specific effect of the preparation It has been maintained that other theophylline preparations for example theophylline with sodium acetate have no effect on periodic breathing while ethylene diamine and some other amines influence the breathing like aminophylline According to our observations however intravenous injections of theophylline sodium acetate act favorably on Cheyne Stokes respiration and we have seen equally good effects when urea was used as a solvent for the theophylline instead of ethylene diamine The explanation of the action of aminophylline in Cheyne Stokes is made more difficult by the recent discovery (Kety) that after injection of this compound the cerebral blood flow is decreased and not increased

Not rarely the patient reports in the morning after having had an evening dose of aminophylline that the night could have been a good one since breathing was much easier than it had been for a long time but he was unable to sleep This is due to the central stimulation by theophylline which may cause consider

able excitement in some patients Therefore the combination of a sedative with aminophylline is often necessary A barbiturate will usually offset the stimulating effect of aminophylline

Morphine and Sedatives Morphine particularly in the form of an injection of 0 01 Gm or more is contraindicated in Cheyne Stokes breathing In fact even in healthy persons morphine causes Cheyne Stokes which in turn also responds well to aminophylline

A useful sedative for cardiac patients although it has been unjustly avoided for many years is chloral hydrate The doses which depress the circulation are much larger than those customarily employed as a sedative and hypnotic Doses of 2 Gm per rectum or smaller amounts in the form of a syrup by mouth are effective and harmless

CARDIAC ASTHMA AND PULMONARY EDEMA

Cardiac asthma and acute pulmonary edema (paroxysmal nocturnal dyspnea) also result from left ventricular failure and patients presenting these phenomena require digitalis Specific therapy is however necessary during the attacks and in order to prevent recurrences until digitalis brings about the desired effect

Morphine The sovereign remedy in these attacks is morphine If given quickly and in sufficient doses it affords immediate relief While the finer mechanism of its action is still unknown one can assume that it helps by di minishing the excitability of the centers

No stimulating effect of morphine on the circulation is known and morphine certainly does not help to relieve an attack of paroxysmal nocturnal dyspnea by improving the circulation Its prompt effect has always given support to those theories of paroxysmal nocturnal dyspnea which assumed abnormal reflexe or an abnormal condition of the respiratory centers as the causal mechanism

Morphine sulphate is usually given hypodermically during the attack and the dose should not be less than 0 02 Gm Since quick action is necessary and absorption from the cold skin and from the subcutaneous tissue may be slow it is better to administer morphine in this dosage intramuscularly Even the intravenous administration of 0 01 Gm of morphine sulphate has been recommend ed It is well to include atropine sulphate in the amount of 0 0005 Gm (½ mg) with the injection of morphine

Morphine also prevents recurrences of the attacks Very small doses suffice to guarantee a quiet night and prevent new attacks of cardiac asthma and pul monary edema An injection of 0 01 Gm of morphine or pantopon or even one tablet or 0 02 Gm of pantopon is given at bed time The most inexpensive method of administration particularly in hospitals is by an aqueous solution of morphine hydrochloride or sulphate The administration of 20—30 drops of a 1 per cent solution usually suffices It has the advantage of rarely causing morphinism at least we have never observed it in many hundreds of cases After a few days the use of morphine usually becomes unnecessary because car diac action has been improved by digitalis

the consequently increased return of blood to the heart is considered one of the major reasons for the nocturnal appearance of the attacks With the legs dangling the circulating blood volume may be reduced by 400 ml Patients in shock however should lie flat or even with the lower part of the body elevated

Aminophylline Aminophylline has also been recommended for the attacks of cardiac asthma There is no doubt that in the absence of pulmonary edema when expiration is prolonged and difficult when a great deal of bronchospasm exists aminophylline may be useful

Atropine Doses of 1—2 milligrams of atropine have also been recommended for decreasing reflex action and preventing secretion This treatment is useful in experimental pulmonary edema One must however be careful in the intravenous administration of large doses of atropine to patients with coronary sclerosis because the increase of heart rate may cause cardiac hypoxia and may have serious consequences For this reason and owing to the disagreeable side effects of large doses of atropine this treatment is not recommended

Hypertonic Glucose Solution Very effective is an injection of a highly concentrated solution of dextrose for example 40 ml of a 40—50 per cent solution The improvement may appear within a few minutes The action is not ascribed to the sugar A purely osmotic effect of the hypertonic solution is responsible

Intravenous injections of sugar with or without insulin have frequently been recommended for the treatment of various heart ailments These injections were supposed to act particularly well in various myocardial and coronary diseases No proof has been advanced as yet of any beneficial effect The introduction of hypertonic solutions into the circulation causes an appreciable increase of the circulating blood volume by withdrawing fluids from the tissues and augments the load for the heart In patients with cerebral edema an increase of the spinal fluid pressure has been observed after an initial fall Therefore the administration of 50 per cent sucrose has been recommended for these cases The cerebrospinal fluid barrier is not permeable for sucrose Hypertonic solutions of sucrose have however an injurious effect on the kidneys

Even if one employs venesection tourniquets or hypertonic glucose solutions no time should be lost in giving morphine as soon as possible This treatment alone is reliable only in the terminal pulmonary edema is it useless

Morphine in Cardiac and in Pulmonary Dyspnea

It was mentioned in the preceding section that morphine is a most effective remedy for cardiac asthma and pulmonary edema It is no less useful in other forms of cardiac dyspnea

For decades morphine was hailed as a second digitalis and was employed very often in cardiac patients At present its beneficial effects on decompensated and dyspneic cardiac patients is often forgotten

In the chapter on dyspnea it was shown that even the form of breathlessness due to pulmonary congestion does not depend exclusively upon the mechanical

effects of congestion but that various reflexes play an important role In this group of patients examination of the arterial blood reveals no hypoxia As long as no pulmonary complications exist the blood is normally saturated with oxygen and contains even less carbon dioxide than normal blood Pulmonary congestion produces reflex hyperventilation This hyperventilation alone may exhaust the patient because the greater physical work of respiration represents an increased burden It also leads to the detrimental effects of excessive exhalation of carbon dioxide (hypocapnia) If small doses of morphine are given to such patients for instance 20 drops of a 1 per cent solution of morphine sulphate in water and the irritability of the centers is reduced slightly the dyspnea diminishes markedly and with it the added work imposed on the circulation Following one dose of morphine to an otherwise untreated patient one can often observe that in addition to the great subjective relief a profuse diuresis may start and the size of the liver may diminish The great restlessness of these patients is abolished and they can be handled much easier The statement of clinicians about 50 years ago namely that compensation may be achieved with morphine alone is certainly true for some decompensated non fibrillating patients

Therefore every decompensated dyspneic cardiac patient should receive small doses of morphine in the morning and evening for the first few days of treatment until the beginning of the digitalis effect makes this treatment unnecessary The small doses recommended do not inhibit diuresis and no danger of morphinism need be feared if these doses are given by mouth for the short time they are indicated

At this occasion it is appropriate to stress the fact that in contrast to cardiac dyspnea all types of pulmonary dyspnea contraindicate the use of morphine In these cases oxygen saturation of the blood is diminished and carbon dioxide retention may also take place due to the pulmonary lesion In this instance the *dyspnea is not the abnormal outcome of various factors connected with decom*pensation but an important phenomenon necessary to maintain life and to compensate for the pulmonary lesion Once the irritability of the respiratory centers is reduced by morphine and the respiration is slowed the exchange of gases suffers and hypoxia with increased cyanosis and hypercapnia appear Patients soon fall asleep the breathing becomes more infrequent longer and longer respiratory pauses appear cyanosis increases and soon death may occur by respiratory standstill

This is not a rare event and such occurrences unfortunately are encountered all *too frequently Often* the connection between the administration of morphine and the death of the patient is not clear to the physician he attributes the fatality to the severe pulmonary process It is regrettable that most of the current textbooks of clinical medicine and even of pharmacology do not stress this contraindication

Morphine must be used with greatest care in cases of severe emphysema and kyphoscoliosis in diffuse bronchopneumonia in bronchial asthma in bilateral

tuberculosis and pneumonia and in diffuse metastatic pulmonary neoplasms In mild emphysema bronchopneumonia tuberculosis or malignancy of the lung morphine may be administered if indicated however in those extensive pulmonary lesions which cause cyanosis or dyspnea morphine is forbidden We have seen patients die within a half hour with the picture just described because inexperienced physicians ordered morphine for severe pain in a patient with carcinoma and extensive pulmonary metastases or advanced pulmonary tuberculosis Patients with bronchial asthma rarely die during an untreated attack This happens however often if morphine is given If for any reason morphine must be administered or the physician is uncertain how much of the dyspnea is of pulmonary origin small doses of the drug or better demerol may be given The patient should be watched carefully so that the centrally acting stimulants like atropine coramine caffeine or aminophylline can be administered promptly if the depression of the respiration becomes more marked Nallin in the amount of 5 to 10 mg is effective

For the same reason in pulmonary edema when copious hemorrhagic sputum is already evident and bubbling rales are audible all over the lungs it is well to omit morphine because a mechanical impediment causes the dyspnea and its suppression may lead to asphyxia Morphine is given in these cases after one succeeds in causing the absorption of the alveolar transudate by an intravenous injection of hypertonic glucose solution or by the use of a high pressure oxygen mask

CARDIAC STIMULANTS

In patients with cardiac weakness preparations of the digitalis or strophanthin group are primarily indicated In some cases for instance in acute cardiac failure of various origins in acute pulmonary edema in pulmonary embolism and right heart failure one may find it necessary to stimulate cardiac action immediately before the digitalis glycosides can show an effect on the heart Sometimes side effects of digitalis like extrasystoles forbid continuation of digitalis even if it is otherwise indicated For this purpose a host of remedies have been recommended but only a few are really useful

Strychnine For many years strychnine was employed as a cardiac stimulant It was early recognized however that strychnine has no effect on the heart and can only be used to increase vascular tone It has been given by mouth or by subcutaneous injection in the dose of 2 mg three or four times daily

Pressor Amines Epinephrine has a very strong action on the circulation It combines a positive inotropic action on the heart muscle with a constrictor effect on the vessels in wide areas of the body Nevertheless its disadvantages are great When given by mouth or by rectum it is practically inert If administered hypodermically its action is sometimes stormy and vanishes in a short time Even small doses are dangerous to cardiac patients due to the resultant marked tachycardia the elevation of blood pressure and the remarkable increase of the oxygen requirements of the myocardium which often cannot be

met Therefore this drug should never be used in cardiac patients even if it seems necessary for other purposes for instance as an addition to a local anesthetic or for the treatment of swollen nasal mucous membranes

Some of the newer pressor amines and substances related to adrenalin however are indicated in cases in which for instance in myocardial infarction during local anesthesia or following sympathectomy the blood pressure threatens to fall to dangerously low levels Paredrine and neosynephrine are given in these cases without undue danger to the heart A single dose of 2 mg of paredrine by mouth or 5—10 mg of paredrine or neosynephrine by intramuscular injection may be used Isuprel (10 mg) may be given sublingually

The action of these drugs is more prolonged and less stormy than that of epinephrine

Camphor Coramine Metrazol Preparations of camphor were greatly cherished by many physicians in various countries as cardiac remedies and were given whenever stimulation of the heart seemed indicated There is however no evidence available to prove a stimulating action of camphor on the heart The same holds for some synthetic preparations which were originally recommended as synthetic camphor like stimulants The best known of these preparations are coramine and metrazol (cardiazol) These preparations have no stimulating cardiac effect nor do they increase contractility of the heart They stimulate medullary centers and only in this way lead to a moderate rise of blood pressure and increased respiration They should not be employed for stimulation of the heart muscle

Xanthine Bodies Several preparations belonging to the xanthine group possess a stimulating effect on the heart They are particularly useful because this effect is combined with vasodilatation and some diuretic action

It has been pointed out before that some of the xanthines like theophylline stimulate the heart muscle Caffeine in particular increases the contractility of the myocardium and increases the amplitude of contraction especially of the damaged or weakened heart The effect on the heart rate varies because this depends on various central and peripheral factors which act in opposite directions

For injection the soluble double salts like caffeine and sodium benzoate are used A subcutaneous injection of 0 25—0 3 Gm may be given every two hours when necessary For oral treatment caffeine purum in doses of 0 1 Gm is useful However strong black coffee which the patient may take much more willingly is no less effective than a capsule or an injection of caffeine The caffeine content of a small cup of coffee may exceed the amount given in a capsule or injection

VENESECTION LEECHES

The effect of venesection on cardiac asthma pulmonary edema and in hypertension was discussed in the corresponding chapters This therapeutic procedure is time honored and purely empirical

Patients with marked venous stasis and hepatic engorgement that is patients with right heart failure seem to derive some benefit from phlebotomy

The removal of 400—500 ml of blood may bring relief The venous pressure may fall temporarily and the patient may improve subjectively The *spinal fluid* pressure also falls (Robertson and Fetter) Usually however a delay of several hours is safe and the same result can be secured by an injection of a mercurial diuretic

In patients with right heart failure in the course of pulmonary disease (decompensated cor pulmonale) phlebotomy sometimes affords excellent results In general however this procedure is rarely necessary and rarely used Simultaneously with a lowering of right atrial pressure venesection causes an increase of cardiac output This may be due to the fact that the heart was over loaded before the phlebotomy and the extreme increase of filling pressure had led to a fall in output

It has been pointed out that phlebotomy is helpful in polycythemia complicating pulmonary vascular sclerosis or congenital heart lesions It helps in plethoric patients with chronic congestive heart failure

When the use of leeches is recommended one often encounters a smile of pity We are however able to confirm the observations of others (Sir Thomas Lewis) that this old method of treatment may be very useful if employed upon definite indications The most important situation in which leeches may bring relief is in patients with an acute engorgement of the liver leading to severe pain *in the right hypochondrium* Under these circumstances the application of three or four leeches over the liver suffices to bring relief in a few hours A demonstrable reduction of the size of the liver may be found afterward Although patients object at first to the use of these unpleasant creatures they report definite relief in every instance when the procedure is employed Nothing definite is known about the modus operandi of this measure It has been suggested that the success may be due to the relation of some vascular spasm within the liver via a cutaneous visceral reflex We found however that irritation of the corresponding section of the skin by cantharides plasters or cupping decidedly less effective

TOTAL THYROIDECTOMY AND OTHER OPERATIONS IN CARDIAC FAILURE

Total thyroidectomy in patients with intractable angina pectoris has been discussed

It has been known for more than 30 years that subtotal thyroidectomy can exert an excellent effect in patients with organic heart disease and mild hyper thyroidism In these patients the signs of decompensation may vanish soon after the operation sometimes the heart even becomes smaller disturbances *of rhythm* disappear and the functional capacity of the patient increases remarkably The postoperative improvement is very impressive since previously intensive therapy with the most powerful agents available often had failed

The occasional observation of similar striking improvement in patients operated on for an assumed hyperthyroidism although subsequent histologic examination of the thyroid revealed no sign of hyperfunction suggested subtotal

thyroidectomy also for cardiac patients without hyperthyroidism (Blumgart Levine) Since the initial improvement in several cases was followed soon by a recurrence of the original symptoms it was recommended that subtotal thyroidectomy should be discarded and that *total* thyroidectomy be performed The recurrence of symptoms after the older procedure was attributed to regeneration of thyroid tissue

The operation was adopted by many physicians with enthusiasm Others repudiated it At the present time it seems to be rarely employed since thyreoidectomy can be accomplished by drugs without surgery

The procedure deserves consideration in a very carefully observed case if in spite of intensive digitalis therapy the use of the modern diuretics and despite constant hospitalization a tolerable state of compensation cannot be maintained When prolonged observation shows that the myocardium of these patients is in good condition and in the absence of the contraindications to be mentioned presently the operation may be tried One should not treat by thyroidectomy a patient in whom decompensation is merely the result of an infection a pulmonary embolism or an arrhythmia In these instances removal of the cause of decompensation furnishes relief in a simpler way No signs of progression in aortitis should be present and no evidence of activity in cases of rheumatic heart lesion

At first the success of the procedure was ascribed to the fall of the basal metabolic rate It was believed that the operation leads to a diminished oxygen requirement in the tissues and thus the demands of the tissues are adapted to the impaired circulation But it soon became clear that the improvement appears before the basal metabolism is lowered indeed occasionally it was evident a few days following the operation Therefore abolition of a direct thyroid effect on the circulation is involved When the basal metabolic rate falls to low levels and evidence of hypothyroidism appears small doses of thyroid are given Sometimes we were able to maintain the basal metabolic rate at a normal level in these patients while the improvement of the circulation remained

One must also consider that fact that with the development of myxedema the cardiac output as well as circulation time fall to lower levels This too forces us to seek for another explanation for the benefit of surgical or chemical thyroidectomy than simply the diminution of the oxygen requirements of the tissues

Another indication for this mode of therapy are patients with paroxysmal tachycardia or paroxysmal flutter and fibrillation who suffer from very frequent attacks and who do not respond to the usual therapy Here diminution of thyroid activity may lessen the severity and incidence of the attacks

Thiourea derivatives proved helpful and were used with advantage in patients with congestive heart failure as well as in patients with angina pectoris However the simplest and for the patient least inconvenient therapy is that with radioiodine The iodine uptake is at first determined with a tracer dose of I^{131} Then doses of 20—30 millicuries are given orally in intervals of 5—6 weeks Often good results are obtained early after the first dose The development of a myxedematous state is by no means necessary

It is claimed that in congestive cardiac failure this therapy helps in about 50 per cent of the cases In angina pectoris excellent results were reported in one third of the cases and worthwhile results in another one third In the latter group we found chemical thyroidectomy particularly helpful in patients with aortic stenosis and aortic insufficiency and decubital angina Recently Blumgart et al reported worthwhile improvement in 75 per cent of patients with angina pectoris and about 60 per cent of patients with congestive heart failure

Other Operations in Congestive Heart Failure

In patients with congestive cardiac failure particularly in mitral lesions Cossio recommended ligation of the inferior vena cava Satisfactory results were reported by him and others (Bernath et al) The operation is contraindicated in high output failure but provided immediate relief in the congestive heart failure of mitral patients

These operations as well as the creation of an artificial experimental tricuspid insufficiency (Cossio et al) are now superseded by direct operation on the cardiac valves

ANTICOAGULANTS IN CONGESTIVE HEART FAILURE

Thromboembolism in patients with congestive heart failure is a common complication and about one third of patients with rheumatic valvular lesions develop heart failure because of pulmonary emboli If — as usually happens — the patient is forced to stay in bed the danger of new embolism is even greater

The thrombi are not only located in the lower extremities but also and even more extensively in the venous plexusses of the pelvis the hypogastric veins the prostatic and ovarian plexusses which we had examined for years in every post mortem examination of patients dying from congestive heart failure and which we found thrombosed in practically every instance

Such pulmonary embolisms coming repeatedly over a prolonged period may by themselves cause heart failure and are detrimental for patients whose hearts are already overburdened because of rheumatic fever or coronary sclerosis

It has often been stated that therapy with digitalis increases the danger of thrombus formation In a careful study of this question Cormsen found no correlation with the degree of diuresis and thrombosis but a good correlation between intensity of therapy and thrombosis

For these reasons prolonged anti coagulant therapy has been recommended in patients with congestive heart failure (Wishart and Chapman Harvey and Finch) and a significant reduction of the occurrence of thromboembolism has been reported Griffith et al found in the treated group an incidence of this complication of 1 8 per cent while it was 15 5 per cent in the untreated group

A final decision on whether or not the measure should be used routinely is not yet possible One will understand that by the use of anticoagulants new hazards are added to those already existing It should appear advisable to wait until

studies covering a large amount of material show that the dangers of the therapy are minor and the advantages outweigh them

DIETARY QUESTIONS

Even if no special diet is required detailed instructions should be given to cardiac patients since the definite advice is always welcome

Compensated cardiac patients in general need not be subjected to great dietary restrictions A normal mixed diet is permissible Foodstuffs which cause flatulence foods which are not easily digested and large meals should be avoided Eat frequently but do not take too much at one time is an excellent precept Fluids should be taken mainly between meals

The dietary requirements in patients with hypertension coronary sclerosis or myocardial infarction have been discussed in the chapters dealing with these conditions

Patients with cardiac failure and edema should receive a diet poor in salt or even salt free Even healthy persons who receive a salt free diet for one day have a profuse diuresis and show a loss of weight surpassing 1 Kg within 24 hours The great contribution of such a diet to the development of a satisfactory diuresis in edematous patients is readily understandable

Recently a high fluid intake has been recommended in cardiac edema (Schemm) It was pointed out that edematous patients may even be dehydrated If the sodium in the diet is restricted and the diet yields a neutral or acid ash remarkable diuresis may be obtained even with administration of more than 4 000 ml of water daily Meat eggs cereal prunes and plums belong to the food stuffs giving an acid ash Milk fruit juices and fruit with the exception of those mentioned above should be avoided Ammonium chloride (3 Gm daily) or a few drops of dilute hydrochloric acid in every glass of water serve to increase the acidity This diet has been abandoned by us and in many other places

The Karell diet consisting of 800—1 000 ml of milk only taken during the day is very satisfactory The use of milk has however some disadvantages Many patients do not like it in many it causes meteorism and distension and in others diarrhea Moreover milk is salt poor and not salt free It contains 750 mg of sodium per liter For this reason raw or cooked vegetables may be substituted for milk All varieties of fruits or vegetables are permissible Even potatoes are allowed particularly for heavy eaters They may be eaten with the skin which on account of their high content of potassium are supposed to exert some diuretic effect The total quantity of fruit or vegetables permitted during 24 hours should not exceed 1 200 Gm No other food and no other drinks are given This diet is followed for three days in succession and then supplemented by proteins

Artificial salts have been devised but most of them have a high content of sodium and are therefore of little value Usually one can dispense with them Garlic pepper paprika vinegar and the like are permitted

In patients who develop marked albuminuria a hypoproteinemia may appear during chronic congestion Therefore a diet rich in proteins is necessary

In patients who are overweight a low caloric intake will be prescribed For most patient 20 calories for one Kg body weight are suggested The calculated ideal weight of the patient rather than the actual weight should serve as a basis for the dietary regime

The amount of liquid permitted to a patient with decompensation should not exceed 800—1 000 ml within 24 hours Naturally fruits vegetables soups are calculated as fluids

Excessive smoking and consumption of large quantities of alcohol are prohibited It has been stressed in the appropriate chapters that in patients with hypertension with coronary diseases and particularly in patients with peripheral vascular diseases smoking is harmful even in smallest quantities while alcohol taken in moderation is useful

AIR TRAVEL CLIMATE

In this era of air travel the question must often be decided whether the patient may undertake a trip by plane With the exception of obvious contraindications such as severe congestive heart failure or a fresh myocardial infarction the answer will most often be yes The small risk is illustrated by the experience (Graybiel) that among 7 million passengers carried by five major airlines only 3 deaths occurred during flight and 5 shortly after landing from cardiovascular disease The rule if you can walk you can fly was accepted but consideration should be given to certain facts

A patient with a myocardial infarction should not fly until four months have elapsed since the day the infarction occurred Dyspneic patients should not fly Among laymen the opinion prevails that pressurized planes are safe however they are pressurized at a level of 7 000—8 000 feet Some patients with angina pectoris need oxygen at 5 000 feet Patients with status anginosus or attacks of angina pectoris at rest (angina de decubitus) should not fly Abdominal distention due to the expansion of abdominal gases often causes discomfort The administration of 1 tablet of dramamine every four hours is recommended

Cardiac patients particularly those with congestive heart failure do not tolerate humid and hot climate well On the other hand even in a subtropical climate patients with angina on effort are more comfortable and the need for nitroglycerin diminishes

The literature on observations on the occurrence of attacks of coronary thrombosis or apoplexy in connection with particular barometric pressures and other climatic factors is large In Dallas Texas the incidence of myocardial infarction during the summer months is greater (Heyer et al) while the incidence in Northern cities seems to be greater in the winter Others reached different conclusions (Schnur) A sudden elevation of atmospheric temperature and humidity may precipitate an attack of left ventricular failure

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emesis gastric lavage and purgation The efficacy of these measures depends upon the site and rapidity of absorption of the poison and the interval between ingestion and attempted removal Such variables as the delayed gastric emptying produced by shock or pylorospasm make it worthwhile to attempt removal in the absence of a contraindication Since prompt removal is essential it is more important to proceed with the means at hand than to wait for special equipment or solutions

Spontaneous *emesis* frequently follows the ingestion of irritants Vomiting may be induced by stimulating the pharynx the administration of gastric irritants (hypertonic saline solution mustard) or by the use of centrally acting emetic drugs such as apomorphine These measures however are often ineffective or contraindicated When patients are stuporous and gagging emetic drugs are usually ineffective and the administration of large amounts of fluid may hasten passage of the poison through the pylorus before vomiting occurs Whenever possible it is better to rely upon gastric lavage than the vagaries of emesis

Gastric lavage is associated with certain dangers It should not be attempted after the ingestion of strong acids or alkalies because of the danger of perforating the injured tissues Clinical judgment must be used in deciding whether the advantages of lavage outweigh its dangers as a stimulus when the patient is convulsing The danger of aspiration can be minimized by positioning the patient with head and shoulders down and the head turned to one side Careful removal of gastric contents in itself reduces the risk of aspiration in the unconscious patient The orogastric tube should be of sufficient size (30 to 40 French) to permit aspiration of particulate matter Passage into the esophagus is facilitated by flexing the patient s neck After the initial aspiration small amounts (in the range of 250 ml) of the lavage solution should be alternately instilled and aspirated The use of larger volumes increases the risk of forcing gastric contents through the pylorus Lukewarm water is a satisfactory irrigating liquid *Universal antidote* (e g activated charcoal 2 parts tannic acid 1 part magnesium oxide 1 part *water 100 parts) may have some* advantages but time should not be lost in its preparation if it is not immediately available In some poisonings lavage with a substance which destroys precipitates dissolves or neutralizes the poison may be of help These agents will be mentioned in the discussion of specific poisons

Following removal of poison from the upper gastrointestinal tract *cathartics* may be used to hasten the passage of the remaining poison out of the lower gastrointestinal tract Saline cathartics such as magnesium sulfate in amounts of 15 to 30 Gm may be left in the stomach following lavage Cathartics in general are contraindicated in strong acid and alkali poisoning

Prevention of Absorption of Topically Applied Poisons Removal of contaminated clothing should be followed by copious flooding of the involved area of skin or mucous membrane with water While organic solvents weak acids or bases may be more effective in certain instances (which will be noted) skin decontamination with water should proceed while they are being obtained Wiping must be gentle to prevent inunction of poison remaining on the skin surface If exposure is limited to an extremity venous occlusion with a tourniquet may be helpful in delaying systemic absorption

Prevention of Absorption of Injected Poison Cruciate incision and suction will remove unabsorbed poison which has been injected but this procedure is rarely feasible except in poisonous bites Absorption can be delayed effectively by the application of cold and tourniquets and by immobilization

Prevention of Absorption of Inhaled Poison Further absorption of toxic gases vapors aerosols and dusts can be prevented by removal of the victim to an uncontaminated atmosphere and by assuring adequate pulmonary ventilation If the casualty cannot be moved a protective mask should be applied

Symptomatic and Supportive Therapy For many poisons no specific antidote is known Therapy must then be directed toward control of manifestations as they appear Even in instances where specific antidotes are available such problems as hypotension and hypoxia must be attacked directly Certain of these manifestations appear with sufficient frequency to justify their brief discussion here

While *coma* is an ominous sign unresponsiveness rarely requires specific therapy per se Concomitant depression of respiratory and vasopressor centers however frequently requires prompt and vigorous treatment if the patient is to survive The comatose patient requires careful observation and meticulous nursing care (p 1770)

Hypotension may arise from any of a number of causes—anoxia depression of the vasopressor centers *autonomic ganglionic blockade loss of blood* water or electrolytes cardiac arrhythmia or myocardial damage Rational therapy is predicated upon correction of the underlying defect Vasopressor amines particularly norepinephrine are helpful in combating the shock produced by central depression and ganglionic blockade In the latter instance the patient is unusually sensitive to vasopressor amines For further discussion of the management of shock see p 1769

Tissue *hypoxia* also may result from varied causes poor pulmonary ventilation secondary to central respiratory depression muscular paralysis

bronchospasm retained secretions or upper airway obstruction impairment of alveolar capillary diffusion due to pulmonary edema deficient oxygen transport as in anemia methemoglobinemia carboxyhemoglobinemia shock and inhibition of cellular oxidation *When the hypoxia is produced* by underventilation the first step is to ensure a patent airway Secretions should be removed by suctioning and any obstruction relieved by the insertion of an oropharyngeal airway endotracheal tube or tracheotomy tube depending upon the site of obstruction If ventilation remains inadequate *despite a clear airway* and oxygen administration or if there is respiratory arrest the patient must be assisted manually or by mechanical means

Pulmonary edema produced by injury to alveoli exposed to irritant gases is less responsive to treatment than the pulmonary edema associated with cardiac failure (p 1307) Therapeutic measures include *suppression* of cough frequent suctioning high concentrations of oxygen under positive pressure aerosols of surface active agents adrenal cortical steroids bronchodilators and if infection complicates the picture antibiotics

The management of *methemoglobinemia* carboxyhemoglobinemia and inhibition of cellular oxidation will be discussed under the specific poisons producing these changes

Convulsions may be produced by a wide variety of poisons The management of seizures is discussed beginning on p 335

Electrolyte imbalance and *dehydration* are frequent sequelae to protracted vomiting and diarrhea In addition to these certain poisons produce more specific defects for example the acidosis of methanol poisoning and the hypocalcemia of fluoride poisoning *these will be described under the appropriate poison*

Acute hepatic insufficiency is the primary manifestation of some poisonings (chlorinated hydrocarbons cinchophen phosphorus and occasionally mushroom poisoning) and its management is described beginning on p 1504

Acute renal insufficiency may appear as a result of such prerenal factors as shock dehydration and electrolyte imbalance or as the result of concentration and excretion of nephrotoxic substances by the kidney When renal failure occurs it should be managed as outlined on p 1367

Cardiac arrhythmias produced by poisons are managed in a manner similar to those otherwise produced (p 1240)

SPECIFIC ANTIDOTAL TREATMENT

Specific antidotal agents fall into three categories First those antidotes which exert their therapeutic effect by *reducing the concentration of the toxic substance* by promoting excretion (e g the administration of chloride or mercurial diuretics in bromism) by combining cyanide with methemoglobin, lead with ethylene diaminetetraacetate or mercury with dimercaprol or by precipitation in the gut (e g the use of sulfate to precipitate certain alkaloids) Second there are antidotes which *compete biochemically* with the toxic substance for its receptor site (e g vitamin K_1 in coumarin poisoning or atropine in muscarine poisoning) Third are those antidotes whose pharmacologic action is antagonistic to that of the poison (e g picrotoxin in barbiturate poisoning) This last type of antidotal treatment merges with symptomatic therapy in many instances

CLINICAL MANIFESTATIONS OF SPECIFIC POISONINGS

In the discussions of specific toxic agents in this chapter many details of drug action have been omitted except where pertinent to the problem of recognition or treatment of poisoning Toxic manifestations due to drug hypersensitivity or allergy are *discussed elsewhere (p 1163) It has been necessary* to eliminate from consideration a large number of toxic materials to which exposure occurs only in specialized industrial procedures Instead emphasis has been placed on toxic agents which may be encountered by the general population In the references at the end of the chapter will be found further details of toxicologic and historic interest

Acetanilid Acetophenetidin Although symptoms resembling salicylate intoxication may follow overdosage of these agents the most prominent finding is methemoglobinemia with dusky cyanosis fatigue *and headache Treatment is symptomatic* (p 1198)

Acids Since strong mineral acids are not commonly found in the home ingestion is usually the result of suicidal attempt Necrosis sloughing bleeding and perforation of the gastrointestinal tract may be produced and chemical burns are usually visible in the mouth and oropharynx These lesions are more charred than the gelatinous burns produced by alkali and can often be differentiated from them by appearance alone Because of the danger of perforation lavage should not be attempted Treatment consists of dilution of the acid neutralization with weak alkali relief of pain and supportive measures if necessitated by shock or loss of blood and fluid Alkalies such as sodium bicarbonate which evolve carbon dioxide should be avoided *because of the possibility* of rupture of an eroded stomach Magnesium oxide or hydroxide and aluminum hydroxide are preferable If weak alkali is not immediately available the ingested acid should be diluted by administering water or milk

As with alkali burns delayed perforation or stricture formation may occur although the latter is said to be less common in acid burns

Aconite (Wolfsbane Monkshood Larkspur) Aconite is the active principle of several members of the larkspur family it is no longer used therapeutically because of its instability in solution Poisoning is usually due to ingestion of one of these plants and is manifested by vagal and peripheral sensory nerve stimulation and medullary depression Pathognomonic is intense tingling without erythema or evidence of inflammation This is followed by nausea vomiting abdominal pain diarrhea bradycardia hypotension visual impairment unconsciousness and death due to respiratory depression Treatment is purely supportive with large doses of atropine (0 5 to 1 0 mg) to counter the vagal effects

Alkali (Lye Drano Sodium Hydroxide, Caustic Potash Potassium Hydroxide, Washing Soda Sodium Carbonate, Potassium Carbonate Household Ammonia Ammonium Hydroxide) The caustic action of lye and other strong alkalies results in deep serious burns and subsequent scarring of the intestinal tract after ingestion The immediate effects of oral ingestion are redness and soreness of mouth and pharynx followed in several hours by sloughing of the mucosa and bleeding The same process occurs in the esophagus and stomach Treatment is directed toward cautious neutralization of the alkali with dilute acetic acid (10 per cent vinegar) Intubation during the acute stages should be avoided because of the likelihood of esophageal perforation In severe cases there is circulatory collapse as a result of pain and fluid loss Occasionally significant respiratory obstruction due to edema of the hypopharynx necessitates attention to the maintenance of airway Pain should be relieved with meperidine (Demerol) or opiates With subsidence of the acute phase of poisoning esophageal dilatation and other measures for prevention of strictures should be carried out Delayed perforation may occur

Aminopyrine (Amidopyrine Pyramidon) Over dosage of this drug may produce symptoms resembling those of salicylate intoxication however the drug is mainly of importance because of the frequency with which its use in therapeutic doses is followed by agranulocytosis presumably because of a hypersensitivity reaction (p 1209)

Amphetamine (Benzedrine Dexedrine) Amphetamine and its isomers are widely abused for their exhilarating effects Besides its sympathomimetic action amphetamine is a cerebral stimulant Symptoms of overdosage are tremor dry mouth anorexia nausea diarrhea irritability hallucinations and severe insomnia Hypertension and angina occur particularly in older patients Although there has been a tendency to regard amphetamine as a relatively harmless stimulant which can be used safely in large amounts in comatose patients such as those suffering from barbiturate poisoning evidence indicates that in doses exceeding 300 mg daily there is danger of precipitation of fatal ventricular arrhythmias Administration at any dosage level should cease with appearance of pulse irregularities Treatment consists of barbiturates for sedation and appropriate agents such as quinidine or procaine amide for the purpose of controlling arrhythmias (p 1240)

Aniline This material is chiefly important as an industrial hazard but its use in certain inks dyes crayons and solvents such as paint removers causes occasional poisoning It is absorbed as the vapor or through the skin and poisoning has occurred in infants from exposure to inks used in marking hospital diapers The main manifestation is methemoglobinemia (p 1198)

Antabuse (Disulfuram Tetraethylthiuram Disulfide) See p 755

Antibiotics See p 814

Anticoagulants (Heparin Dicumarol Warfarin) See p 1268

Antihistamines The widespread and unsupervised use of antihistamines makes them readily available for accidental overdosage and suicidal attempts There is wide individual variation in tolerance to these drugs Death due to respiratory depression followed ingestion of only 200 mg of diphenhydramine in one adult while 2 000 mg produced only impaired mentation in another In children the usual toxic manifestations are excitement and convulsions followed by central nervous system depression In adults depressive manifestations predominate with lethargy coma and pupillary dilatation although convulsions followed by further depression can occur Initial treatment should be directed toward removal of unabsorbed drug and the maintenance of adequate respiration and blood pressure Analeptics should be avoided if there is hyperreflexia Should convulsions occur they may be controlled with an ultra short acting barbiturate such as thiopental or with ether to avoid deepening postictal depression Occasionally patients intoxicated with antihistamine drugs which have prominent atropinelike properties may manifest toxic delirium fever mydriasis dry mouth and urinary retention (see Atropine)

Antihypertensive Drugs Toxic effects of drugs used in the treatment of hypertension are described on p 1329

Antimalarial Drugs See p 1113

Atropine (Hyoscyamine Scopolamine Hyoscine Belladonna Stramonium Deadly Nightshade Jimson Weed) When these drugs have been used poisoning is due to therapeutic overdosage in sus

ceptible patients the intranasal use of ophthalmic solutions or to ingestion of plants containing one of these alkaloids There are many so called "solanaceous" plants which contain alkaloids whose action resembles that of atropine or scopolamine

The manifestations of overdosage of atropine are those of parasympathetic blockade central nervous system excitation followed by depression dryness of mucous membranes dysphagia burning of eyes and throat with intense thirst dilated and inactive pupils tachycardia marked flushing and dryness of the skin hoarseness strangury restlessness talkativeness mental confusion and hallucinations progressing to mania Terminally coma and circulatory collapse occur

With scopolamine the pulse is slow there is no flushing of the skin and central nervous system depression with lethargy and somnolence is seen rather than excitement of the type produced by atropine The Babinski response is said to be present in scopolamine poisoning but absent after atropine

Treatment consists of sips of water instillation of mineral oil into eyes and nose to moisten mucous membranes and the use of methacholine or pilocarpine to relieve peripheral symptoms However in the presence of a high degree of block these parasympathomimetic drugs have little or no effect Indeed the absence of effect following the subcutaneous injection of 5 or 10 mg methacholine will confirm suspected poisoning with belladonna alkaloids Gastric lavage should be performed after oral ingestion With atropine cautious sedation may be necessary with scopolamine mild stimulation with caffeine or amphetamine combats depression Catheterization is usually necessary Hyperthermia may occur particularly during hot weather because of inability to sweat If the patient survives for 24 hr death is unlikely but manifestations may persist for several days especially after an overdosage of atropine

Barium Poisoning occurs chiefly from ingestion of rodent poisons containing barium carbonate Rarely soluble barium salts have been given by mistake for x ray purposes in place of the insoluble barium sulfate Barium acts as a stimulant to contraction of all types of muscle producing tremors and spasm in skeletal muscle and hypertension due to arteriolar spasm Its action is particularly pronounced on the intestinal tract where it is manifested by nausea vomiting and abdominal cramps Death usually occurs from increased myocardial irritability with ventricular fibrillation Muscle weakness persists for several days after recovery from acute poisoning Treatment consists of gastric lavage and administration of Epsom salts (to precipitate the barium as insoluble sulfate) supportive measures and the use of quinidine or procaine amide to reduce the danger of fatal cardiac arrhythmia

Benzene Exposure to this solvent occurs chiefly from its use in industry but it may enter the home as a component of dry cleaning solutions paint remover or rubber cement In very large doses it acts as an anesthetic but its chief danger arises from bone marrow depression Susceptibility to this poison appears to vary greatly and exposures which are safe for most people may cause fatal disease in a few Treatment is directed toward the hematologic defect (p 1209) and *complete* protection from further exposure

Beryllium See p 1407

Bleaching Solutions (Sodium Hypochlorite Clorox Purex) The ingestion of sodium hypochlorite solution causes corrosion of the mucosa of the oropharynx and upper gastrointestinal tract Local burning nausea and vomiting are produced Laryngeal edema may occur Lavage with sodium bicarbonate solution is indicated (weak acids should *not* be used) Perforation and stricture formation are rare

Bromides The bromide ion is a central nervous system depressant Although seldom prescribed by physicians at the present time it is still found in many proprietary headache remedies and "nerve tonics" Despite efforts in recent years to curtail the sale of bromides chronic bromide intoxication or bromism is still relatively common Acute poisoning is rare because vomiting commonly follows ingestion of a single large dose However with continued administration bromide accumulates in the body and symptoms of intoxication appear These symptoms are caused by the bromide ion itself and are not a reflection of the decrease in chloride caused by displacement Bromide is handled in the body like chloride being excreted almost entirely via the kidneys although tears sweat and gastric juice also contain the ion Rapid tests for blood bromide are available Although it is generally stated that a blood bromide level of 200 mg per 100 ml (25 mEq/liter) results in the appearance of symptoms higher levels are sometimes well tolerated and severe intoxication is often seen with lower quantities In general the finding of a level of 75 mg per 100 ml (9 mEq/liter) or more must be regarded as confirmatory of the diagnosis of bromism if the clinical picture suggests it

Symptoms range from drowsiness lethargy and dysarthria to coma or mania with psychotic behavior Many patients suffering from bromism were committed to mental institutions in the past Often bromides were prescribed for control of symptoms of unrecognized bromide intoxication A blood bromide determination is indicated in any patient with unusual mental symptoms or unexplained lethargy particularly if a history of drug ingestion is elicited Various types of skin eruptions ranging from acneform lesions to proliferative nodular

lesions not unlike those of tertiary syphilis are also produced by bromides but more than 75 per cent of patients with mental symptoms due to this drug have no dermatitis

Treatment consists of sedation (paraldehyde being the drug of choice) careful nursing and removal of the source of bromide Chloride displaces the bromide ion and promotes its excretion chloride administration may be pursued vigorously but in general with cessation of bromide ingestion and mild chloride supplementation (2 to 4 Gm NaCl three times daily) symptoms subside readily and tremendous doses of sodium or ammonium chloride seem worthwhile only in extreme cases The administration of mercurial diuretics hastens elimination of the drug by promoting a bromide as well as chloride diuresis Hemodialysis with the artificial kidney hastens the excretion of the poison and is probably advisable in severe cases if the necessary equipment is available

Caffeine Although human fatalities due to caffeine are rare overdosage leads to insomnia mild delirium tinnitus tachycardia and prominent diuresis Because caffeine has a direct effect upon the myocardium it may cause serious arrhythmias and dosage should be limited to 6 Gm daily A cup of coffee contains 100 to 150 mg of caffeine The excitatory effects are easily controlled with barbiturates

Camphor Formerly a popular stimulant this drug is now rarely used therapeutically however occasional cases of poisoning are still seen as a result of ingestion of liniment or moth flakes Manifestations are headache sensation of warmth confusion clonic convulsions and terminal respiratory depression The characteristic odor of camphor facilitates the diagnosis Treatment is supportive Barbiturates should be used with caution in combatting convulsions because of postictal respiratory depression Camphor is closely related to thujone formerly the active principle of absinthe which was probably responsible for convulsions in absinthe addicts

Cantharides (Spanish Flies Blistering Beetles Essence of Viper) Poisoning may follow accidental ingestion but is probably commonest after taking cantharides powder for abortion or as an aphrodisiac often as a prank It is a potent irritant and vesicant Symptoms are severe burning pain in the mouth esophagus and abdomen intense thirst bloody diarrhea and hematemesis The vomitus contains shining particles if the powder has been taken There is rapid onset of acute urethritis with painful micturition priapism oliguria hematuria anuria with uremia delirium and death Treatment consists of gastric lavage avoidance of oils or fats (the active principle is fat soluble) morphine for pain and tenesmus and blood and fluid replacement With anuria which is due to glomerular necrosis a regimen for acute renal failure (p 1367) might offer hope for recovery although clinical data on such a trial are lacking

Carbon Monoxide Carbon monoxide is a colorless odorless gas formed by incomplete combustion of carbon containing materials It is a component of manufactured illuminating gas and automobile exhaust fumes and with the exception of alcohol is the most common cause of poisoning treated in hospital emergency clinics The effects of carbon monoxide arise from its ability to form a stable compound with hemoglobin (carboxyhemoglobin) reducing the oxygen carrying capacity of the blood Symptoms include decreased exercise tolerance headache irritability reduced judgment and memory confusion collapse and unconsciousness The symptoms may all appear within a few minutes or may develop gradually if exposure is minimal but prolonged Carboxyhemoglobin is bright red and patients show a characteristic cherry colored flush Cyanosis is absent Treatment is directed toward the breakdown of carboxyhemoglobin by adequate ventilation in the presence of high oxygen tension The patient should therefore be removed from exposure immediately and oxygen inhalation should be instituted Recovery is usually rapid but if tissue anoxia has been prolonged irreversible nervous system damage may have occurred

Carbon Tetrachloride (and Other Halogenated Hydrocarbons) Halogenated hydrocarbons are widely used as industrial solvents Inhaled in sufficient concentration all are capable of inducing narcosis and in addition have varying amounts of hepatic and renal toxicity Household exposure to carbon tetrachloride may occur through use of safe (noninflammable) cleaning solvents or fire extinguishers Absorption may occur following inhalation of fumes in a closed space (3 ml evaporated in a room $10 \times 10 \times 8$ ft yields the maximum safe concentration of 25 ppm) percutaneous absorption or ingestion Renal involvement is said to be more common after inhalation than after ingestion which leads to absorption by the portal venous system The toxic effects of this solvent are greatly enhanced in alcoholics Manifestations are abdominal pain nausea vomiting diarrhea and headache within a few minutes followed in hours or days by progressive damage to liver or kidneys or both The renal lesion can progress to complete anuria with proper fluid management and possibly the use of the artificial kidney survival is possible despite this complication Hepatic damage may be acutely progressive with severe jaundice and rapid death The hepatic lesion is a severe central necrosis Death secondary to pulmonary edema common in the past was due to excessive fluid intake in anuric patients rather than any toxic action on the myo

cardium Spraying carbon tetrachloride on an open flame results in the production of phosgene an even more toxic substance which produces pulmonary edema There is no specific therapy other than gastric lavage and stimulants Management of the renal lesion (p 1367) and a regimen designed to minimize the hepatic damage are indicated

Castor Beans (Ricin) Poisoning by ricin an extremely toxic protein is usually a result of ingestion of castor beans by children Castor bean plants are often raised as ornamental shrubs in this country *Ricinism* is characterized by nausea vomiting and profuse diarrhea with severe dehydration beginning several hours after ingestion of the beans Occasionally convulsions and respiratory depression are a cause of death but the usual picture is one of somnolence progressing to coma Weakness is extreme If the patient survives the acute symptoms there may be anuria and uremia with death after several days There is evidence that this renal lesion is due to a direct action of the poison but the early development of dehydration is undoubtedly an important factor also Ricin has the property of agglutinating erythrocytes in vitro It is uncertain whether this occurs *in vivo* but isolated clinical reports of intravascular clotting make it seem likely that it can play a role in the development of symptoms

Treatment consists of fluid replacement sedation or stimulation as indicated and management of anuria (p 1367)

Chloral Hydrate Poisoning due to this sedative is now rare Differentiation from barbiturate poisoning is usually possible only by history although miosis is said to be commoner with chloral poisoning In addition to its action as a central nervous system depressant chloral exerts a direct toxic effect upon heart liver and kidneys particularly in the presence of preexisting disease Patients who survive death due to respiratory depression during the first few hours may become icteric and die with acute yellow atrophy within a few days Tolerance to chloral rarely develops indeed sudden increases in susceptibility to its effects may result in signs of poisoning in patients taking doses previously well tolerated Chloral is a strong gastric irritant and gastritis is prominent in habituated individuals usually chronic alcoholics There is probably no basis for stories of its potentiation by alcohol in "mickey finns

Colchicine Poisoning is due to accidental ingestion or therapeutic overdosage in the treatment of gout Several hours after oral ingestion, nausea vomiting diarrhea (occasionally bloody) and abdominal pain appear There are progressive weakness and lethargy ascending paralysis with normal mental status and terminal convulsions Death is due to respiratory depression Hematuria and anuria are common but usually transient Treatment is symptomatic

Coramine (Nikethamide) Poisoning due to Coramine is always the result of acute parenteral overdosage and is manifested by intense itching, sneezing and rarely convulsions Duration of action is so short that therapy is seldom indicated although barbiturates may occasionally be helpful

Croton Oil This drastic cathartic has no therapeutic use but poisoning by ignorant pranksters is occasionally seen Croton oil is a strong irritant producing vesiculation and pustulation if applied directly to the skin and a severe hemorrhagic gastroenteritis within 1 to 3 hr after ingestion Death is the result of dehydration blood loss and shock A dose of 20 drops has been fatal for an adult Treatment is supportive with copious parenteral fluids blood replacement and morphine to quiet the bowel

Cyanide Hydrocyanic acid a very volatile material and its sodium or potassium salts are among the most rapidly acting poisons known Hydrocyanic acid is sometimes used for fumigation Cyanide salts are widely used in industry and may reach the home in photographic chemicals or as ingredients of certain types of silver polish Cyanide has a typical bitter almond odor (and has the property in extremely minute concentrations of giving tobacco smoke a peculiar taste chemists working with cyanides often smoke during their exposure to facilitate recognition of minute leaks of the gas into the atmosphere) The fatal dose is small—as little as 300 mg salts or 100 mg hydrocyanic acid gas may cause death Cyanides exert their physiologic effects by combining with iron-containing enzymes such as the cytochromes and catalase with the result that hydrogen and electron transport are blocked (p 463) the energy releasing mechanisms of metabolism cease and death occurs from tissue asphyxia Since the metabolic block is in the tissues rather than the blood the hemoglobin is saturated with oxygen and cyanosis is not seen until respiratory depression supervenes Symptoms depend on the mode of entry of the toxic material When inhaled absorption is so rapid that death may be almost instantaneous hydrogen cyanide has been used for the execution of criminals Oral doses act more slowly requiring several minutes before the appearance of symptoms and as much as an hour for death As the blood cyanide level increases there is headache ataxia nausea profound dyspnea palpitation convulsions and unconsciousness The diagnosis is suggested by the odor of bitter almonds and by the history of abrupt catastrophic onset Treatment must be instituted immediately to be of value The objective is to bind the cyanide in harmless form as the highly stable cyanmethemoglobin This is accomplished by the production of

methemoglobinemia by inhalation of amyl nitrite perles (one every 2 to 5 min unless blood pressure is below 80) followed by intravenous injection of 10 ml of 3 per cent sodium nitrite over a 2 to 4 min period Since speed is essential inhalation is preferable to injection in initiating treatment The use of methylene blue has been advocated but its action is too slow to be of great benefit although it may be given if nitrites are not available The production of methemoglobinemia should be followed by the slow intravenous injection of sodium thiosulfate (50 ml of a 25 per cent solution over a 10 min period) to convert cyanide liberated from the dissociation of cyanmethemoglobin to thiocyanate Norepinephrine or epinephrine may be necessary to maintain blood pressure particularly with the added hypotensive effect of nitrites After nitrites have been given supportive measures may be instituted but unless a considerable degree of methemoglobinemia is produced promptly the outlook is not improved by other forms of treatment

Cyanide is rapidly destroyed in the body by oxidation to relatively harmless thiocyanate If therefore the patient survives a few hours recovery is likely After the acute episode is over there may be residual cerebral symptoms

DDT (*p* Dichlorodiphenyltrichloroethane Chlorophenothane and *Similar Insecticides*) This common ingredient of insecticide powders sprays and aerosols is poorly absorbed unless dissolved in a vehicle such as kerosene or carbon tetrachloride but under these circumstances it readily enters the body through the skin lungs or gastrointestinal tract Fatal poisoning has occurred from the absorption of 150 mg per kg body weight The other related chlorinated diphenyl insecticides and the chlorinated indane insecticides (aldrin Chlordane dieldrin heptachlor) produce toxic manifestations similar to those of DDT Lindane (hexachlorbenzene) produces more striking liver damage The symptoms of acute poisoning are central nervous system hyperexcitability delirium and convulsions followed by progressive depression with paralysis coma and death In chronically exposed patients cerebellar symptoms and evidence of liver damage may develop Treatment consists of gastric lavage barbiturate sedation support of respiration and the alleviation of muscle contractions by intravenous injection of calcium salts Epinephrine should probably be avoided since animal studies indicate an increased susceptibility to epinephrine induced ventricular fibrillation with DDT intoxication Ingestion of fats should be avoided for several days The potential toxicity of the vehicle in which DDT is dissolved should be remembered

Digitalis See p 1312

Ergot (Ergotamine Ergonovine) Poisoning is usually due to illegal use as an abortifacient or to therapeutic overdosage The latter is likely to occur in patients with severe infection liver disease or hyperthyroidism which conditions are contraindications to the use of ergot derivatives Symptoms are nausea and vomiting (relieved by atropine) diarrhea burning abdominal pain (if orally ingested) weakness of legs tingling of extremities severe muscle pains (relieved by massage and calcium gluconate) psychotic behavior and finally convulsions coma and ischemic peripheral gangrene The vascular effects are due to a combination of prolonged vasoconstriction and obstructing intimal hyperplasia and thrombosis Treatment is supportive using nitrites papaverine and mechanical procedures designed to restore circulation and morphine for pain which is often very severe

Favism Ingestion of fava beans or inhalation of its pollen by sensitive individuals results in an acute hemolytic anemia Susceptibility to favism seems to run in families although the disease sometimes appears with no family history of favism often in patients who have eaten the beans for many years Treatment is purely supportive with transfusions etc (p 1187) The disease is rare in this country but has been common in Mediterranean countries particularly Italy

Fluoride *Fluoride salts* are the chief toxic ingredient of many insect poisons When kept in large quantities especially in institutional kitchens they have been mistaken for baking powder or table salt and added to food producing large epidemics of intoxication Fatal poisoning occurs after the oral ingestion of about 2 Gm of the sodium salt Fluoride acts in three ways in the presence of an acid medium e g the gastric contents it forms hydrofluoric acid an exceedingly corrosive material it combines with plasma calcium forming insoluble calcium fluoride causing tetany and it also blocks the glycolytic degradation of glucose thus inhibiting carbohydrate metabolism in the initial steps (p 462) Symptoms are nausea vomiting of corrosive material diarrhea and abdominal pain As the ionized plasma calcium falls muscular hyperirritability progresses from increased reflex activity (positive Chvostek) to fasciculations and convulsive tonic spasms There is circulatory collapse and death usually several hours or rarely several days after ingesting the poison Diagnosis is confirmed by the presence of tetany by the fact that blood drawn from patients poisoned with fluoride clots poorly and by the presence of a high blood glucose concentration The hydrofluoric acid in vomitus may etch glass containers The stomach should be washed at once with lime water calcium chloride or calcium gluconate The skin of the face and perineum should be protected from the corrosive gastrointestinal contents Tetany can

be alleviated and some of the fluoride ion bound harmlessly by the constant slow intravenous injection of very large volumes of 10 per cent calcium gluconate or 1 per cent calcium chloride The infusion rate should be adjusted so as barely to prevent a positive Chvostek sign The hyperglycemia is not reduced by administration of insulin Despite these measures mortality is high in fluoride poisoning The chronic ingestion of fluoride in moderate amounts (20 to 100 mg per day) produces mottling of dental enamel (fluorosis)

Formaldehyde Poisoning due to this substance which is a component of various germicides and fumigants is usually diagnosed by the characteristic odor of formaldehyde in the vomitus Manifestations are largely those of gastrointestinal irritation with nausea vomiting abdominal pain tenesmus difficult micturition and central nervous system depression leading to coma There is striking reduction in plasma carbon dioxide–combining power presumably the acidosis is similar in etiology to that seen after methyl alcohol Treatment is supportive with gastric lavage using dilute ammonia and parenteral infusion of large amounts of sodium bicarbonate or lactate to combat acidosis The fatal dose is about 30 ml

Gases Most fire fighters or victims who are "overcome by smoke are in fact poisoned by carbon monoxide and respond rapidly to oxygen inhalation In some instances however burning material releases irritant fumes either by combustion or by the destruction of containers in which dangerous chemicals have been stored Most of the irritant gases thus released cause *immediate* chemical burns of the upper respiratory tract and exposed skin Ammonia nitrogen oxides (which form nitric acid with water) hydrogen sulfide and sulfur dioxide or trioxide (which form sulfurous and sulfuric acids respectively when hydrated) are chiefly dangerous for their local effects Several hours after exposure has been terminated and when the patient appears comfortable severe pulmonary edema may develop This is usually a result of inhalation of nitrogen dioxide or of phosgene which is released when carbon tetrachloride fire extinguishers are played on hot surfaces One should therefore watch carefully for complications in patients who have been exposed to smoke or burning fumes Treatment includes administration of oxygen control of cough and use of steam inhalations

Gasoline and Kerosene Exposure to the fumes of gasoline in high concentration may lead to headache vertigo unconsciousness with typical muscle jactitations convulsions and death from respiratory depression Treatment consists of administration of oxygen and control of seizures with barbiturates

Oral ingestion of gasoline or kerosene is almost invariably followed by bronchopneumonia the management of which is the main therapeutic problem

Glycols The glycols are dihydric alcohols which are sweet to taste and impart a warming sensation when swallowed Propylene glycol is widely used as a vehicle for drugs and flavoring extracts and is relatively nontoxic Ethylene and diethylene glycol are commonly used in permanent antifreeze compounds and are poisonous Both are metabolized to oxalate in the body Poisoning often results from intentional drinking of antifreeze for supposed alcoholic content Ingestion of ethylene glycol is followed by nausea vomiting deep coma bradycardia clammy skin hypothermia and various neurologic findings such as nystagmus anisocoria absent reflexes and convulsions There is no specific treatment although calcium may be given intravenously in an attempt to reduce the oxalate level Death almost always occurs within 48 hr after massive ingestion from respiratory failure or pulmonary edema

Diethylene glycol produces severe hepatic and renal necrosis with jaundice anuria and uremia Because of the striking renal changes mercury poisoning is often mistakenly suspected in these patients Management of anuria by attention to electrolyte balance etc as for any lower nephron nephrosis (p 1367) appears to be a reasonable therapeutic approach since the renal lesion is reversible

Insecticides and Rodenticides These toxic substances are commonly found in the home and are responsible for a significant number of fatal accidental and suicidal poisonings The clinical manifestations produced depend upon the active ingredients and in some cases upon the toxicity of the solvent Management is discussed under the active ingredients and solvents

Insulin See p 628

Iodine Acute poisoning may follow ingestion of 1 0 ml tincture of iodine or of Lugol s solution and five times this amount may be fatal There is burning abdominal pain nausea and vomiting pallor collapse rapid pulse albuminuria and oliguria Death may occur after an hour or may be delayed for a week Salivation conjunctivitis and edema of the eyelids appear after a few hours Vomitus is blue or black if the stomach contains starch Treatment consists of gastric lavage with starch solution (the blue product is nontoxic) the injection of 10 ml of 10 per cent sodium thiosulfate intravenously every 4 hr to reduce free iodine to less toxic iodide and supportive measures Patients taking iodine for suicidal purposes rarely succeed

Small doses of iodides produce salivation lacrimation coryza fever swelling of the eyelids swelling and tenderness of the salivary glands (iodide

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dation of carbohydrate with the consequent accumulation of acid intermediates

Symptoms of poisoning are visual disturbance nausea abdominal pain muscle pain dizziness weakness and various disturbances of consciousness ranging from deep coma to clonic seizures Visual disturbance is almost universal and ranges from mild blurring to total loss of light perception Often impairment of vision is transient although as is well known permanent blindness may follow survival of the acute symptoms Abdominal pain is excruciating and is probably due to pancreatitis which is commonly seen at necropsy Serum amylase is elevated and many cases have been erroneously thought to have surgical disease of the abdomen Likewise cerebrovascular accident is often suspected in sporadic instances of methanol coma Kussmaul respiration may occur but is absent in many severely acidotic patients Abdominal tenderness and spasm are striking and there may be rigidity of the neck Eye findings are helpful the pupils are dilated and nonreactive and ophthalmoscopic examination usually shows typical hyperemia of the optic disk with retinal edema There is no true papilledema and vessel changes are not characteristic

Death in severely acidotic patients is due to cessation of respiration in the phase of inspiration Circulation is often well maintained for several minutes after breathing stops

Treatment consists of intravenous infusion of alkali in large amounts Five per cent sodium bicarbonate is convenient and effective Plasma carbon dioxide–combining power is rapidly restored by this procedure and symptoms of impaired vision abdominal pain etc are dramatically relieved Return of acidosis is frequent and additional alkali may be needed consequently continued observation of patients is advisable Gastric lavage is useless and administration of alkali by mouth is uncertain in nauseated patients Despite considerable experimental evidence indicating that ethanol inhibits the oxidation of methanol to formic acid limited clinical trials of ethanol in preventing acidosis have not seemed beneficial Although administration of whisky or brandy is permissible alkalinization is the mainstay of treatment and should be instituted immediately Overtreatment alkalosis often occurs but is not dangerous and is preferable to undertreatment The eyes should be protected from light until acute symptoms subside

The use of barbiturates to control convulsions and various stimulants such as caffeine or amphetamine is helpful but these procedures are only of transient benefit and correction of acidosis is the primary aim of therapy

Metrazol Poisoning manifested by convulsions is due to therapeutic overdosage and is amenable to barbiturates So violent are convulsions after Metrazol that fractures are a common sequel

Milk Sickness (Snakeroot Richweed Rayless Goldenrod) The ingestion of these plants which contain *trematol* produces the disease in domestic animals known as trembles Human poisoning can result from eating the plant but is most frequent after consumption of the milk or meat of poisoned animals Manifestations are weakness stiffness of the legs anorexia nausea and prostration The tongue and mucosal surfaces are reddened and the breath smells strongly of acetone Circulatory collapse and unconsciousness occur terminally Transient recovery with relapse is common Biochemically there is acidosis acetonuria hypoglycemia and rise in NPN particularly of guanidine The mechanism of action is not clear Death rarely occurs in less than 48 hr and symptoms can persist for several weeks Gastric lavage is useless because symptoms appear after a latent period of several hours Treatment consists of administration of carbohydrate and supportive measures Alcohol was long advocated as an almost specific antidote but there is no basis for its use in therapy

Moth Balls (Paradichlorobenzene Naphthalene) (See also Camphor) These substances are relatively nontoxic except when prolonged massive exposure by inhalation has occurred Under these circumstances they produce central nervous system depression Cataracts have been reported after severe chronic exposure and paradichlorobenzene can produce liver damage if sufficient quantities are absorbed Both materials are relatively safe if swallowed and no specific therapy other than gastric lavage is needed although naphthalene in the form of moth balls or toilet bowl deodorant has been reported a number of times as causing hemolytic anemia after ingestion

Mushroom Poisoning (Mycetismus) There are many poisonous mushrooms but in this country most poisoning is due to *Amanita muscaria* or *Amanita phalloides* After ingestion of *A muscaria* which contains muscarine there is rapid onset of parasympathetic stimulation nausea vomiting diarrhea salivation perspiration lacrimation bradycardia dyspnea with increased bronchial secretion wheezing expiration dilated pupils confusion and excitability Illness begins within 6 hr after eating the mushrooms Recovery usually takes place within 24 hr

Amanita phalloides contains a hepatotoxin and is far deadlier than the muscarine type Six to fifteen hours after eating there is explosive onset of violent abdominal pain vomiting and bloody diarrhea with rapid dehydration and extreme thirst The pupils are normal Within 24 hr in the majority of cases there is onset of jaundice and anuria and death from acute yellow atrophy can occur within

mumps) and skin rash in susceptible individuals Whether these manifestations of *iodism* are due to hypersensitivity or idiosyncrasy to the direct action of the drug itself is not definitely established

Isopropyl Alcohol (Isopropanol Rubbing Alcohol) The diagnosis of isopropyl alcohol intoxication is usually made by its characteristic odor or the finding of an empty bottle of this substance It is approximately twice as toxic as ethyl alcohol and produces profound unconsciousness not unlike that produced by large amounts of its ethyl homologue Coma rarely lasts longer than 8 to 14 hr and treatment with mild stimulants and intravenous fluids is all that is indicated The only threat to life is the irritating action in the stomach which makes vomiting with aspiration a great danger gastric lavage is indicated in all patients Transient acetonuria is common (isopropyl alcohol is oxidized to acetone in the body) but significant acidosis is not seen If intravenous glucose has been given and glycosuria is present the patient may be thought to have diabetes although the confusion is soon corrected by observation of the patient s subsequent course There are no sequelae significant bleeding from gastritis has been reported to complicate convalescence

Local Anesthetics (Procaine Cocaine, Pontocaine Nupercaine Etc) The many drugs in this group vary greatly in toxicity but manifestations of overdosage are so similar that a single description will suffice Poisoning is almost always due to parenteral use of concentrated solution intended for topical use or to overdosage caused by confusion of names Many persons are abnormally susceptible to local anesthetics and manifest symptoms with small doses of procaine the least toxic of the group In sufficient amounts these agents are toxic to the heart and respiratory center and stimulate the central nervous system Mild reactions consist of dizziness dyspnea and pallor In severe poisoning there are convulsions circulatory collapse mydriasis and respiratory failure which may supervene within a period of a few minutes Treatment consists of artificial respiration injection of large doses (0 5 to 1 0 ml) of epinephrine and intravenous injection of a short acting barbiturate Because barbiturates almost specifically counteract the toxic effects of local anesthetic premedication with one of this group of sedatives is advisable before the use of these drugs

Addiction to cocaine in the United States is usually found in individuals who also take morphine The cerebral stimulation produced by cocaine is transient and is soon outweighed by the other effects of the drug The use of cocaine is said to stimulate addicts to crimes of violence It is almost always used by intravenous injection rather than as the old fashioned snuff

Magnesium The magnesium ion is a profound depressant of the central nervous system and of neuromuscular transmission Poisoning is usually due to parenteral administration of magnesium sulfate for hypertension or occasionally to oral or rectal use particularly in patients with renal impairment Manifestations of poisoning are disappearance of reflexes fall in blood pressure hypothermia stupor and respiratory failure Magnesium is toxic for the myocardium but significant cardiac depression is preceded in human beings by respiratory failure The treatment is intravenous administration of a calcium salt which immediately counteracts the untoward effects of magnesium This antagonism between calcium and magnesium on neuromuscular and autonomic ganglionic transmission is due to their reciprocal effect on acetylcholine release

Marihuana (*Cannabis sativa* or Indica Hashish India Hemp Reefers) This narcotic is smoked for *its intoxicating and exhilarating effects* The sequence of events after exposure is not unlike that seen with alcohol but there is more of a tendency to disorientation hallucinations paranoia and particularly a loss of sensation of passage of time The material does not produce tolerance but smokers may become dependent on it for emotional support Overdoses produce severe depression and coma but death is unusual There is no specific treatment The effects are of short duration

Mescaline (Peyote Mescal Buttons) This drug is derived from a species of cactus and is used by Southwestern Indians for ceremonial purposes Its ingestion produces symptoms very similar to those of acute schizophrenia There are colorful pleasurable hallucinations loss of time sense and mild anesthesia Pupils are dilated and there may be bloody diarrhea and unconsciousness after large doses Death is due to respiratory failure There is no treatment other than a supportive regimen

Methyl Alcohol (Wood Alcohol Methanol) Although industrial exposure by inhalation was formerly a hazard methyl alcohol poisoning is now due almost entirely to its ingestion as a substitute for ethanol The toxic dose is extremely variable death has resulted from a dose as small as 20 ml whereas 200 ml has been ingested with survival Methanol is oxidized in the body slowly to formic acid via formaldehyde and the manifestations of poisoning are believed to be due to accumulation of these toxic metabolites This is borne out by the presence in most cases of a lag period of 12 to 24 hr between ingestion and onset of symptoms

The prime manifestation of poisoning is severe acidosis which is not fully explainable on the basis of accumulation of formic acid alone at present the best theory seems to be that formate exerts an inhibitory effect upon enzymes involved in the oxi

An excellent sedative this drug rarely produces respiratory depression even in tremendous dosage (up to 120 ml) although patients may remain unconscious for as long as 48 hr after overdosage Treatment is supportive Morphine and paraldehyde should be used together cautiously because of increased toxicity of this combination Habituation to paraldehyde is occasionally observed among chronic alcoholics who hope to prevent delirium tremens by its use

Phenol and Cresols (Lysol) Poisoning is usually due to ingestion with suicidal intent Diagnosis is facilitated by the characteristic odor of phenol or Lysol Manifestations of poisoning are the same but Lysol requires larger doses for a fatal effect Although poisoning with phenol may cause death within 30 min death may be delayed many hours These substances produce severe erosion of the mucosa of mouth throat esophagus and gastrointestinal tract the burned areas having a characteristic dead white appearance There is vomiting and later diarrhea often with bleeding An initial stage of excitement is followed by coma circulatory collapse and respiratory depression Convulsions are commoner in children than in adults If the patient survives long enough small amounts of urine which darken on standing may be voided Later anuria due to tubular necrosis develops There is often severe acidosis with profound reduction in plasma carbon dioxide—combining power The mechanism of this acidosis is unknown but it may involve some defect in enzyme function such as is seen in methanol or formaldehyde poisoning

Treatment is directed toward removal of the unabsorbed poison by gastric lavage and preventing obstruction of the glottis by edema due to the pharyngeal burns Laryngoscopic inspection should be carried out early and intubation performed if necessary to maintain the airway Rarely tracheotomy may be needed The stomach should be washed with olive oil Because phenol is soluble in ethyl alcohol and alcohol is by far the best substance to use in removing phenol from the skin it is often recommended as a lavage fluid However in contrast to olive oil alcohol will speed the absorption of phenol and is definitely contraindicated for lavage Other treatment consists of infusion of 5 per cent sodium bicarbonate intravenously to combat acidosis (this often produces dramatic improvement) replacement of blood and the use of stimulants and measures to combat shock if blood pressure falls

Chronic exposure to phenol results in pruritus pigmentation of the skin paresthesias and gastrointestinal disturbances Occasionally discoloration of the cartilages similar to that in ochronosis is seen

Phosphorus Elemental phosphorus occurs in several allotropic forms Of these only one yellow phosphorus is appreciably toxic It is an ingredient of certain rat poisons The use of phosphorus in the manufacture of matches has been outlawed as a result of poisoning which occurred in workers in match factories and because of numerous instances of accidental poisoning in children The exact fatal dose is not known

There is burning of the mouth and throat after ingestion and a garlic odor is noticeable on the breath Abdominal pain and vomiting soon become intense When sufficient quantities have been ingested the vomitus glows in the dark Often symptoms subside after a few hours but after 24 to 48 hr *subacute* effects on the liver become apparent and jaundice develops rapidly Death from acute yellow atrophy can occur in a few days

Treatment consists of introducing 100 ml of 1 per cent copper sulfate solution into the stomach and performing gastric lavage The removal of the copper by lavage is imperative After subsidence of acute symptoms a protective regimen for the liver should be instituted and patients should be observed for several days

Picric Acid Poisoning by picric acid can occur from systemic absorption after application to extensive burns from accidental ingestion of solutions or ointments or from exposure in industrial plants Oral ingestion leads to severe gastroenteritis with yellow vomitus There may be hemolysis liver necrosis or acute glomerular damage with hematuria and oliguria in severe cases Picrate is also a central nervous system depressant in large doses Treatment consists of gastric lavage and administration of egg white or cheese (to form insoluble protein picrates) fluid replacement and symptomatic management of gastroenteritis A regimen for acute renal shutdown (p 1367) should be instituted if anuria occurs High concentrations of picrate on the skin produce a severe itching eczema known as picric itch

Picrotoxin Poisoning due to therapeutic overdosage of this drug produces convulsions which are controllable with barbiturates administered intravenously

Pokeroot (Phytolacca) Poisoning is due to ingestion of the root or bark of this plant as a home remedy for arthritis its leaves and berries are innocuous Within 2 hr nausea vomiting and diarrhea occur They are followed by drowsiness vertigo and blurred vision In fatal cases death results from convulsions and respiratory paralysis Treatment is purely supportive and should include gastric lavage if the patient is seen early

Quinidine See p 1242

Salicylates (Aspirin Sodium Salicylate Methyl Salicylate Oil of Wintergreen) The derivatives of salicylic acid are used in larger amounts by the laity and by the medical profession than any other

4 days Recovery is slow after this type of poisoning

Treatment consists of fluid replacement atropine in doses of 0 6 to 1 0 mg in the muscarinic type and barbiturates for persistent excitement Morphine may be required for relief of pain

Mussel Poison During late spring and summer the common Pacific coast mussel sometimes contains a highly toxic material which produces illness and death within a few hours after ingestion of the shellfish It has been determined that the toxin which is not destroyed by cooking is actually a component of certain dinoflagellates which form the diet of the mussel Similar poisoning has been reported in other parts of the world Manifestations which come on within a few minutes are paresthesias of the oral mucosa and extremities progressing to complete anesthesia weakness incoordination ataxia dysarthria and progressive central respiratory depression Circulatory collapse is secondary to hypoxia Survival for 12 hr indicates a good prognosis for life but complete recovery may be prolonged for weeks Treatment consists of gastric lavage the use of artificial or mechanical respiration and supportive measures

Nicotine This alkaloid is an ingredient of many insecticides Poisoning may occur from 150 mg or less equivalent to a few drops of nicotine sulfate (Black Leaf 40) by mouth or inhaled The action of nicotine is a complex mixture of depression and stimulation of the autonomic system and depression of the central nervous system Symptoms consist of gastrointestinal irritation combined with dizziness headache and tachycardia Cortical irritability culminating in convulsions and myocardial irritability with arrhythmias precede death which is usually the result of cardiac or respiratory arrest Although atrophine will counteract many of the peripheral autonomic disturbances (salivation miosis blurred vision) caused by nicotine it is ineffective in preventing respiratory or cardiac failure Supportive treatment directed toward maintenance of oxygenation and prevention of arrhythmias (p 1240) is therefore of great importance

Nitrites These compounds are of importance chiefly because of their ability to produce methemoglobin (p 1198) While these materials are usually administered therapeutically (the nitrites as amyl nitrite or nitroglycerine) accidental poisoning occasionally occurs from contamination of poorly capped wells with nitrate producing soil bacteria

Nitrogen Mustards See p 1226

Organic Phosphate Insecticides Numerous newly developed insecticides including Parathion (*diethyl p nitrophenyl thiophosphate*) TEPP (*tetra ethyl pyrophosphate*) HRTP (hexaethyl tetraphosphate) OMPA (octamethyl phosphoramide) EPN (ethylphenyl p nitrophenyl thiophosphate) Systox (diethyl 2 ethyl mercaptoethyl thiophosphate and Mipafox (bis monoisopropylamino fluorophosphine oxide) are potent inhibitors of cholinesterase and have been responsible for fatal poisoning in man No deaths yet have been attributed to Malathion a similar anticholinesterase insecticide These materials are usually prepared for use by dilution with inert powder organic solvents or water They are rapidly absorbed by inhalation through intact skin or by ingestion Since cholinesterase destroys the acetylcholine liberated by the central nervous system autonomic ganglions parasympathetic nerve endings and motor nerve endings symptoms are produced by the persistent action of acetylcholine at these sites Clinical manifestations of poisoning are blurring of vision and miosis rhinorrhea salivation sweating nausea vomiting abdominal cramps diarrhea dyspnea tightness of the chest bronchospasm bronchorrhea cyanosis muscular cramps and fasciculations followed by flaccid paralysis convulsions coma and respiratory depression Management consists of removal of contaminated clothing and gentle cleansing of the skin with soapy water Application of a tourniquet will delay systemic absorption from a contaminated extremity Atropine will block parasympathetic and central neural effects It should be given promptly and in large doses (1 to 2 mg intravenously) This dose may be repeated at 3 to 8 min intervals until parasympathetic manifestations are controlled (miosis often persists even with adequate atropinization) After control of symptoms the interval between doses is judged by return of mild symptoms Total doses as large as 20 mg per day are often necessary for severe poisoning Since atropine has no effect on the muscular paralysis artificial respiration may be necessary Careful attention should be paid to the removal of bronchial secretions Barbiturates may be required if convulsions persist despite full atropinization Patients who survive for 24 hr usually recover without residua although symptoms may persist for several days

Oxalates Poisoning from oxalates occurs chiefly from ingestion of ink eradicators or stain removers containing oxalic acid They produce burning of the mouth nausea vomiting and abdominal pain Later formation of insoluble calcium oxalate produces hypocalcemic tetany Anuria from blockage of ureters by calcium oxalate has been reported Treatment of acute poisoning consists of the oral and intravenous administration of calcium salts (e g calcium gluconate or chloride) and a supportive regimen

The leaves of rhubarb contain large amounts of *oxalic acid* and acute poisoning has followed their ingestion

Paraldehyde The diagnosis of paraldehyde poisoning is made easy by its characteristic odor

indicated as for any comatose patient Morphine which is a medullary depressant but a spinal cord stimulant is contraindicated

Sulfonamides See p 814

Turpentine Turpentine is readily absorbed from the skin intestine or lungs and is excreted in the urine which is said to have an odor of violets Chronic exposure to turpentine leads to urethritis a common symptom among painters Ingestion of large amounts (usually for its supposed abortifacient effect) produces colic nausea vomiting diarrhea delirium ataxia and coma If the acute stage of poisoning is survived there may be painful micturition albuminuria hematuria and on occasion anuria and acute renal shutdown due to tubular necrosis Treatment is supportive a regimen for anuria should be instituted (p 1367) since the renal lesion is reversible

Vitamins A and D See pp 525 and 527

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medication Therapeutic poisoning usually results from the cumulative effect of prolonged high dosage for rheumatic fever arthritis of other types etc but accidental poisoning or suicidal attempts account for an appreciable number of cases There is considerable variation in susceptibility to the toxic effects of salicylates idiosyncrasy is common but instances of great resistance are also seen Toxic symptoms may begin at dosages of 3 to 4 Gm per day or may not appear when as much as 10 Gm per day is given The plasma salicylate level is almost always greater than 10 mg per 100 ml when symptoms appear and the development of hyperventilation usually reflects a level of over 40 mg per 100 ml The earliest manifestations are vertigo tinnitus and deafness These signs may subside if treatment is interrupted briefly or even if administration is continued If overdosage continues nausea vomiting headache and various types of mental aberration develop Occasionally there may be great excitement restlessness and talkativeness —the so called salicylate jag At this point the patient usually shows the typical salicyl dyspnea Both vomiting and hyperventilation are due to an effect of the salicylate directly on the central nervous system Early in the development of the syndrome serum electrolytes and the carbon dioxide-combining power are usually normal but as increased urinary loss of alkali compensates for the respiratory alkalosis there is progressive diminution in both serum sodium and carbon dioxide-combining power As this stage is reached there is usually a mild ketosis the result of dehydration and starvation After ingestion of a single large dose of salicylates the development of symptoms may be extremely rapid so that the stage of dehydration ketosis and hyponatremia is reached within a few hours Laboratory examination shows albuminuria hematuria and a false positive ferric chloride test for urinary ketone bodies Experimentally salicylates have been shown to produce hypoprothrombinemia and occasional instances of increased bleeding due to salicylates have been reported in man However salicylate hypoprothrombinemia is uncommon and is not a regular manifestation of poisoning by these drugs Treatment consists of stopping salicylates and of fluid replacement Vitamin K is indicated if there is evidence of excess bleeding Since the reduction in serum sodium is actually a manifestation of alkalosis hypertonic saline solution is helpful However sodium bicarbonate is advocated particularly because it reduces the renal threshold for salicylates enhances excretion and thereby shortens the clinical course Hemodialysis with an artificial kidney has been used with success Although the mortality from therapeutic salicylate poisoning is small it has been as high as 50 per cent in a small series of accidental or suicidal intoxications Methyl salicylate poisoning is particularly dangerous in children who are often attracted by the smell of wintergreen

"Smog" This slang term is used to describe dense fog in which smoke and chemical fumes are also present It is usually merely irritating but under special circumstances industrial waste gases such as hydrogen sulfide sulfur dioxide or the nitrogen oxides may introduce a definite risk of poisoning Although morbidity is sometimes high only among elderly patients with chronic cardiac or pulmonary disease is there danger of death Treatment is removal from the smoky environment If this is impractical the use of an oxygen tent or mask may prevent serious difficulties in susceptible patients

"Smoke" A large number of paint removers lacquer thinners antifreezes and other solvent mixtures are ingested at one time or another for their supposed alcohol content Because of their milky appearance when diluted with water these mixtures are referred to as smoke in many localities although other names are used Some wholly unknown component of these materials occasionally causes a profound hypoglycemia with coma clammy skin and bizarre neurologic signs This disturbance should be considered in any alcoholic who remains stuporous after the usual treatments for alcoholic coma have been tried The injection of 50 per cent glucose intravenously produces dramatic results in these patients and should not be delayed until the suspected diagnosis can be confirmed by laboratory test Patients should be observed carefully for a few hours after treatment because hypoglycemia may recur

Strychnine Poisoning often results from ingestion of A S and B cathartic pills by children eating poisoned grain or suicidal attempts The effect of strychnine is to increase the irritability of the entire nervous system and prolong the period of hyperexcitability after a normal stimulus The patient remains conscious and acutely aware of his surroundings After a period of heightened irritability and muscle twitching tonic seizures occur in which there is opisthotonos rigid extension of the legs facial tetanus producing the *risus sardonicus* and apnea due to spasm both of the diaphragm and of muscles of the abdomen and thorax Each convulsion lasts 1 to 2 min Death from anoxia may follow two to five seizures

Barbiturates should be given rapidly to control convulsions and hence prevent anoxia and death Secondary measures such as lavage etc must await sedation for any stimulus may set off a seizure Observation for 24 to 48 hr is necessary any sign of increased irritability calls for more sedation During this period supportive care is

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patient at first apathetic becomes stuporous and then deeply comatose as the temperature rises The skin remains hot and dry throughout but striking and abrupt changes in color may occur The flushed appearance which is usually striking in the early stages may suddenly be replaced by a grayish pallor Such a change indicates the onset of circulatory collapse and the imminence (or presence) of irreversible damage to vital structures This alteration in the color of the skin is associated with other striking alterations in the clinical pattern The circulatory state is initially that of increased cardiac output (full bounding pulse high pulse pressure prominent visible arterial pulsations exaggerated heart sounds) This state changes to that characteristic of peripheral circulatory failure (Chap 17) Congestive heart failure may occur in patients suffering from preexisting cardiac disease or in persons treated with excessive amounts of fluid by the intravenous route

Hyperpyrexia produces extensive parenchymal damage in the various organs Petechial hemorrhages occur diffusely and especially in the brain and in the skin Patients surviving the disorder may display for prolonged periods clear indications of cerebral cardiac renal or hepatic injury Of particular interest is the neurologic disorder If the patient survives the heat stroke he may be left with a remarkable degree of cerebellar ataxia This first becomes manifest as he emerges from coma and for a time there is a mixture of confusion slurred speech and inability to stand and walk With further recovery the patient's mind usually becomes clear and the cerebellar ataxia is then observed in almost pure form It may be permanent

The *pathogenesis* of the disorder remains obscure The visceral damage is clearly the result of the hyperthermia *The Purkinje cells of the cerebellum* are particularly vulnerable to high temperature The immediate cause of death is peripheral circulatory failure in most instances but may be heart failure in the case of patients given too much intravenous fluid at too rapid rates The sudden onset of peripheral circulatory failure is apparently due to the replacement of the initial circulatory adjustment—visceral constriction with cutaneous dilatation—by visceral dilatation with secondary cutaneous constriction The decline in cutaneous blood flow now participates in the vicious cycle The elevation of metabolism due to the hyperthermia causes further rise in temperature The initial inability to lose heat by evaporation of sweat is now complicated by inability to lose heat by radiation to the surrounding air because insufficient blood is flowing through the skin

The rise in body temperature is clearly due to the cessation of sweating The unsolved question involves the mechanism of the sudden cessation of sweating Certain individuals with congenital or acquired disorders of sweat glands have marked impairment of the capacity to sweat and must avoid hot weather Fatigue of the sweat glands appears to be the responsible mechanism in most instances

The *diagnosis* of heat pyrexia is usually made readily With the exception of intracranial disorders the condition is the only common cause of a temperature higher than 42 C (108 F) in an adult It is the only common condition in which *the combination of a rising temperature and a hot dry skin* is seen The only conditions likely to cause confusion are other causes of high body temperature but in almost all these the skin is either dry cold and pale (in the stage of rising temperature) or moist warm and flushed (in the stage of sustained or declining fever) It is a wise rule to consider all adult patients observed during very hot weather with a temperature of 41 C (106 F) or more to be suffering from this disorder unless another cause can be demonstrated immediately It is far better to treat an occasional patient who does not have heat pyrexia than to fail to institute immediate therapy when this condition is present

The proper management of heat pyrexia depends upon the realization that *the damage done to vital structures by a given level of hyperthermia depends on the time factor* A certain temperature for a certain time may produce irreversible alterations while the same temperature for a shorter time may lead only to reversible ones During periods of excessively hot weather all hospitals should keep a tub filled with water and ice The moment a patient with a temperature of 40.5 C (105 F) or more who also has warm and dry skin enters the hospital he should be immersed in this tub and *given massage to promote vasodilatation and heat* loss After the rectal temperature reaches 38 C (100 F) the patient should be removed to a bed and the temperature measured every few minutes wet sheets and a fan being employed if it tends to rise again or warm blankets if it declines below the normal level It has been shown in controlled experiments on animals that immersion in ice water is definitely superior to the evaporative management in terms of the all important objective of producing rapid decline in body temperature and there is strong evidence that the same conclusion is valid *in human beings*

When peripheral circulatory failure exists after the temperature has been reduced to a normal level intravenous fluids are indicated but with due consideration of the facts that many of the elderly patients with the disorder have diminished myocardial reserve and that heat pyrexia has been shown to impair the functional integrity of the heart When heart failure supervenes as is occa

sionally the case digitalis and the other procedures valuable in treating rapidly developing heart failure (Chap 226) are indicated

The prognosis is very grave in patients with heat stroke but the immediate and rapid reduction of body temperature often saves lives which would otherwise be lost

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105 HYPOTHERMIA AND COLD INJURY

Albert R Behnke and Ralph W Brauer

The employment of low temperature to induce hypothermia in surgical patients for the purpose of reducing blood flow and oxygen requirements of organs has been a noteworthy development in recent years It has been possible by this means to perform operations on the heart brain and even the liver which heretofore have not been feasible Advancements in physiologic techniques are making possible requisite basic studies of oxygen requirements and blood flow to the brain liver (Brauer technique) and other organs when cryo-procedures are employed

It has been possible to reanimate without residual injury small animals with body temperatures cooled to the freezing level (Andjus Smith Lovelock) In the cooled animal cardiorespiratory function and the electrical activity of the brain are brought to cessation and as much as 33 per cent of the total body water may be solidified into ice crystals Of immediate practical application is the fact that frozen hamsters did not develop frostbite in the extremities unless manipulation or mild trauma was inflicted when the animal was in a state of cryorigidity (Smith)

Meryman has outlined the two avenues of approach in freezing biologic materials without injury viz (1) slow freezing with extracellular crystal formation and a resultant high concentration of electrolytes attending the extraction dehydration and (2) rapid freezing forming intracellular crystals sufficiently small so as to be benign In slowly frozen blood it appears to be dehydration and electrolyte concentration and not ice crystal formation which produce hemolysis (Lovelock)

With respect to cold injuries progress may be exemplified by the Korean (U S Army) studies and the investigations in Alaska by Irving and Scholander The following treatises may be cited "Physiology of Heat Regulation and the Science of Clothing" edited by Newburg and "Temperature and Human Life" by Winslow and Herrington A systematic elucidation of the acute effects of cold particularly the role of cold as a prime nonspecific stressor agent is to be found in Selye s book "Stress" The Arctic Institute has prepared six volumes to date which serve as source material the Macy Foundation Conferences on Cold Injury (proceedings edited by Ferrer) also provide source material Finally analysis of physiologic problems especially valuable for physicians will be found in the monograph by Burton and Edholm A detailed clinical study and analysis of the immersion foot syndrome has been made by Ungley

Physiologic Considerations and Tolerance Limits *Vasoconstriction and Dilatation* The effects both physiologic and pathologic of cold are inextricably bound up with the two major responses of blood vessels viz vasoconstriction and vasodilatation Unchecked or exaggerated they are associated either with tissue anoxia or with fulminating vascular reactions destructive of tissue

The immersion of fingers in ice water will demonstrate the relationship between vasoconstriction and pain and the periodic relief afforded by the local oscillatory vasodilatation and constriction the hunting phenomenon of Sir Thomas Lewis Blood flow in the extremities after reaching minimal values between 15 and 18 C (59 to 64 4 F) is greatly augmented apparently through arteriovenous shunts at temperatures between 0 and 8 C (32 to 46 4 F) In this temperature range arterialized blood can be withdrawn from the veins of the hand previously immersed in ice water Blood flow in the chilled

appendage can be greatly modified by warming or cooling the body as a whole (Spealman)

Blood and Metabolic Changes Lung ventilation rate arterial pressure and pulse rate parallel oxygen consumption with a rise during the euphysiologic state and a fall when compensation is broken as in immersion hypothermia

Blood volume changes increased viscosity of blood hemoconcentration diuresis (apparently under posterior pituitary control) and increased hormonal activity are factors influencing the course of cold injury Cold stimulation of the thyroid and adrenal glands may represent the acute response of unacclimatized animals or individuals very similar to the stimulation induced in unacclimatized individuals subjected to altitude hypoxia

Limits of Tolerance to Cold The opportunity to study participants during swimming trials (1955) in the English Channel by Pugh and Edholm and others focuses attention upon the remarkable ability of the trained athlete to maintain a normal deep body temperature for periods of 15 hr or more under conditions in which water and skin temperatures (about 15 C 59 F) are some 38 F lower than deep body temperature Such factual data lend support to the useful concept of a body core insulated by a body shell With vasoconstriction operative in cold water a virtual cut off of peripheral circulation serves to maintain deep body temperature by minimizing loss of heat and to effect what amounts to an autotransfusion There is great individual variability in heat loss when the body is immersed in cold water A relatively obese swimmer for example maintained a normal rectal temperature for 2 hr without shivering when he was immersed up to his neck in water with a temperature of 16 C A lean man under the same conditions despite violent shivering experienced a fall in rectal temperature of several degrees and had to be assisted from the water tank because of partial incapacitation from rigor In water colder than 10 C (50 F) man cannot produce sufficient heat to maintain thermal balance for long periods and cooling proceeds rapidly toward temperature levels that cause serious functional impairment

A skin temperature of the fingers of about 10 C (50 F) is the lower limit for the maintenance of a reasonable degree of manual dexterity in unacclimatized persons On the other hand Eskimos have been known to perform some remarkable manipulative feats with their bare hands at specific tasks in subzero weather

In hypersensitive persons exposure to ordinary degrees of cold may produce immediate or general reactions such as asthma hives vascular spasm vomiting neuralgia convulsions and syncope the latter apparently by a histaminelike effect on capillaries with pooling of blood in the periphery Many of these patients can be desensitized by gradual exposure to cold or by subcutaneous injections of histamine The subject of cold agglutinins is a matter for reference

ACCLIMATIZATION The nice distinction has been made by Hart (cited by Burton and Edholm) between *acclimatization*—changes in the responses of an organism produced by continued alterations in the environment *acclimation*—alterations related to changes in a lifetime and *adaptation*—changes occurring during a period of several generations

Although some primitive peoples live at zero or even subzero temperatures wearing little or no clothing it has not been possible to provide conclusive data on human beings at these temperatures (though it has for lower animals) which clearly distinguish between the acclimatized and even the adapted individual compared with the unacclimatized person (Such data are available for human beings with regard to heat acclimatization) Polar explorers have reported appreciably decreased clothing requirements relative to time of stay in the cold atmosphere Moreover the winter comfort zone as defined by the American Association of Heating and Ventilating Engineers shows a decrease of some 5 F in winter temperatures compared with the summer level Healthy individuals following infancy are remarkably tolerant to acute exposures in cold air or water in the benign range of temperature and living in relatively cold rooms (60 to 65 F) has been consistent with good health and not attended by the respiratory difficulties associated with an indoor air environment of 80 to 85 F during the winter season

Immersion Hypothermia It is convenient to divide responses in cold water immersion into three stages (1) stimulatory—deep body temperature (DBT) normal to 35 C (95 F) (2) depressant—DBT 35 to 30 C (3) critical—DBT 30 to 25 C (86 to 77 F) Apparently 30 to 25 C may be a critical zone since it is possible to cool small animals to 0 C (Andjus and Smith)

Cardiovascular Responses With respect to cardiovascular responses of individuals immersed up to the neck in cold water (5 to 15 C) the initial vasoconstriction is followed by a slight rise of rectal temperature and a transient rise in blood pressure and heart rate The heart rate then decreases in response to the action of low temperature on the pacemaker In contrast with the bradycardia associated with the inhalation of oxygen at normal or at high pressures bradycardia due to low temperature is not abolished by atropine or vagotomy Bradycardia is a striking response to hypothermia

At rectal temperatures of 30 C (86 F) arrhythmias may appear and auricular fibrillation is common When the deep body temperature reaches a level of about 25 C (77 F) there occurs in the dog

a precipitous fall in blood pressure and death supervenes at about 22 C from ventricular fibrillation Of interest are experiments on dogs in which Lian and subsequently Riberi and Shumacker blocked the sinoauricular area with procaine and thereby lessened myocardial irritability and the occurrence of ventricular fibrillation It is the depression of metabolism that renders hypothermia of value in surgery Blood flow and oxygen consumption may be reduced to about 25 per cent of the normal resting level (heart rate 15 to 20 beats per minute) in the DBT range of 25 to 30 C (77 to 86 F) In dogs Rosonoff and Duncan found that cerebral blood flow decreased in proportion to the temperature fall from 35 to 25 C (DBT) there was a two thirds reduction of blood flow to the brain

Employment in Surgery Hypothermia is a crucial procedure but it is possible to deprive vital organs—e g the heart—of blood for periods up to 10 min followed by recovery of normal function (Lewis) The time of exposure to the low temperature must be limited and a great deal more knowledge than now available is required before the procedure is generally acceptable

Hypothermia can be induced with light anesthesia and surface cooling by means of air water or blankets through which brine is circulated at freezing temperatures French physiologists (Laborit Huguenard) on the assumption that the above outlined procedure is traumatic attempted to provide pharmacologic means to induce hypothermia more smoothly through the administration of multicomponent solutions containing either chlorpromazine or certain hydrogenated ergot alkaloids A review of 1 100 cases in which chlorpromazine was used as an adjunct to premedication is given by Lear Chiron and Pallin

Rewarming With respect to rewarming following hypothermia Burton and Edholm conclude that the proper procedure is to restore normal body temperature either slowly or by rapid rewarming (water bath 45 C) There is no middle course In acute immersion experiments there is no question about the beneficial effects of rapid rewarming in water 45 C (113 F) during the initial recovery period to circumvent the further drop in DBT caused by cold peripheral blood lowering the temperature of the body core When the peripheral tissues are warm however the individual should be removed from the bath even though DBT is below normal in order to forestall circulatory collapse from vasodilatation and excessive diversion of cardiac output to the periphery Following long periods of immersion the over all applicability of rapid rewarming is not conclusive because of the probability of depletion of liver and cardiac muscle glycogen and of large fluid shifts resulting in a greatly decreased blood volume In therapeutic hypothermia (Talbott) when low rectal temperatures of 25 to 27 C were maintained for as long as 48 hr rewarming was carried out at room temperature

Local Cold Injury If the injurious responses to cold are divided into freezing (frostbite) and nonfreezing (immersion foot) types of injury then Meryman's diagram (Fig 135) outline differences and similarities in both types of injury The two types of injury may be observed in the same extremity or in different extremities in the same individual e g trench foot or freezing in the hands and nonfreezing in the feet of shipwreck survivors Moreover it is important to recognize as pointed out by Ungley the differences in clinical appearance signs and symptoms underlying pathologic derangements and sequelae of the two entities which may require divergent courses of therapy The diagnosis of freezing versus nonfreezing injury can be made generally on the basis of history and clinical signs and symptoms in the two conditions For classical descriptions of the nonfreezing type of injury or immersion foot syndrome reference is made to the excellent papers of White and of Ungley

Immersion Foot In this entity observed in shipwreck survivors or in soldiers (trench foot) whose feet have been wet but not freezing cold for prolonged periods there is primarily injury to nerve and muscle tissue with essentially no gross or irreparable pathologic changes in blood vessels and skin The clinical picture is in harmony with the results to be anticipated from primary hypoxic trauma and lends itself to a description of three clearly recognizable states (1) ischemia denoted by a pale pulseless extremity (2) hyperemia denoted by a bounding pulsatile circulation for example in red swollen painful feet and (3) a post hyperemic recovery period The initial cold induced vasoconstriction increased blood viscosity and impaired oxygen transport in the ischemic state are augmented by such factors as undernutrition general hypothermia dehydration and trauma from relatively fixed pendent extremities The problem of rewarming pertains to these patients during the stage of ischemia when overheating of tissue may lead to gangrene In the stage of hyperemia the red swollen feet require judicious cooling as indicated by White and by Ungley

It may be helpful to consider this type of injury as a peripheral neuropathy following chilling (Ungley) i e as giving rise to manifestations of the Raynaud syndrome essentially free (to be sure in the state of hyperemia) from the vascular restriction and occlusion seen in Buerger's disease In its mildest form it can be induced in the feet for example in whole body immersion experiments of only 1 hr duration when the bath temperature

appendage can be greatly modified by warming or cooling the body as a whole (Spealman)

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which render routine therapy inadequate and to be acquainted with the benefit and promise of spasmolytic agents and procedures and of judicious ambient temperature regulation In addition there emerge three important admonitions

1 Avoid trauma to the cold extremity including tight dressings manipulation and massage

2 Leave blisters intact

3 Observe absolute conservatism in any surgical procedure calling for amputation

Sequelae of Frostbite Injury Of the 5 600 cold injury casualties evacuated from Korea during the winter 1950–1951 it was possible for Blair Schatzke and Orr to report on a follow up of 100 patients 4 years following injury Although 90 per cent were gainfully employed about 50 per cent were in some measure handicapped Signs and symptoms associated with mild to fourth degree injury were cold feet (in winter) pain numbness excessive sweating abnormal color and impairment of joint mobility The physical findings in patients who had a diagnosis initially of third and fourth degree injury were scars tissue loss and abnormal nails With the exception of hyperhydrosis the chronic injury may be similar to that produced by ionizing radiation Specific roentgenologic changes in bone were cystlike defects near the joint surfaces in the fingers and toes

It should be emphasized that although the physical findings were negligible following first and second degree injury the pain sweating of extremities and paresthesias were as intense as in the severely injured patients The symptoms in these cases may be looked upon as real not psycho compensatory but it would require refined functional tests to elicit abnormalities in these individuals

Prevention of Cold Injury The painstaking indoctrination and training of personnel and the excellent equipment now available should minimize future cold injury in American military units Emphasis is to be placed however on the elimination of individuals susceptible to cold injury and especially on the "hardening and disciplined training possible only in cold environments Although adaptation requires perhaps a period of several generations to confer on inhabitants of Patagonia the ability to exist with little protection in subzero weather nevertheless the degree of acclimatization possible over a period of months through proper training and graded exposure to cold should render resistant individuals who would otherwise become casualties The nature of cold disability *makes prevention mandatory* There is no specific treatment as yet for the mass disorganization and even disintegration of the biologic economy brought about by cold

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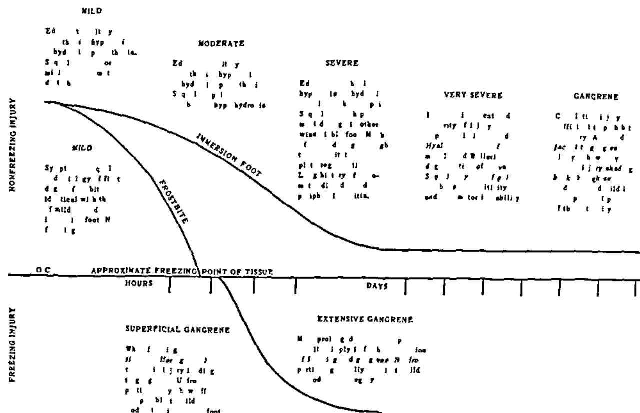


FIG 135 Time temperature relationship in clinical cold injury

is about 8 C (46 4 F) Under these conditions intense vasoconstriction renders the toes exceedingly painful and it is highly probable that the subsequent paresthesia of the feet described as burning sensation which may persist for several years without functional impairment is the result of the ischemia induced during exposure by vasospasm

Frostbite In true frostbite in contrast with immersion foot blood vessels may be severely or irreparably injured the circulation of blood ceases and the vascular beds of the frozen tissue are occluded by agglutinated cell aggregates and thrombi The *cutaneous injury consists in part of a separation* of the epidermal dermal interface From his experiments Kreyberg makes the distinction between direct injury to cells caused by cold which may not be irreparable (if rapid rewarming serves to shorten the duration of the exposure to cold) and the subsequent fulminating vascular reaction *and stasis which precede tissue necrosis* In the therapy of frostbite medical and surgical measures to relieve vasospasm and restore circulation are of prime importance Rapid rewarming may be the method of choice with due concern for the initial elevation of DBT It would appear to serve no useful purpose to heat a cold extremity if the vascular bed cannot accommodate an adequate blood supply In small animals whose extremities have been rapidly cooled to extremely low temperatures within a matter of minutes rapid rewarming is the method of choice when ice crystals are present in tissues It has not been proved convincingly to be so in soldiers whose feet have been exposed to wet cold over a period of *days at freezing* and non freezing temperatures

With *respect to therapy* Korean *experience* interdicted smoking made bed rest mandatory prescribed antibiotics vitamins and nicotinic acid (100 mg t i d) An intravenous frostbite solution consisting of 12 ml ethyl alcohol 250 mg procaine *hydrochloride and 5 per cent glucose in water to* make 250 ml was given every 6 hr To this solution 100 mg heparin was added before administration in the absence of bleeding injury Of the vasodilator drugs hexamethonium was the most effective

One might conclude pessimistically that except *for terminating* the cold exposure promptly and providing good supportive care and later medical and surgical treatment little of value can be done in treating cold injury Yet it is necessary to recognize the type and underlying derangements of the cold injury one is confronted with to be aware of the fact that cold injuries produce a galaxy of ever changing physiologic and pathologic states

to compress the rib cage to a volume that is progressively less forces blood and tissue fluid into the alveoli

The difficulties projected by unequal pressure are seen further in an individual under water who is breathing into a tube opening above the water surface The relative "negative" pressure in the respiratory tract under these conditions is conducive with prolonged respiration to the development of pulmonary edema in much the same process as takes place during the course of edematous obstruction of the trachea from irritant gases or other causes

Effect of Pressure Differences on Ears (Aerootitis Media) Sinuses (Aerosinusitis) and Teeth (Aerodontalgia) In a similar manner aural and sinal membranes are injured by a "squeeze" if the corresponding ostiums of the lined spaces do not permit the free ingress of air In diving operations inability of the auditory tubes to accommodate rapidly to pressure changes occurs in about 10 per cent of apparently healthy individuals About 1 5 per cent of individuals experience sinal pain and another 1 5 per cent are subject to pain in teeth in which the pulp is diseased presumably from bubbles which form more readily in inflamed tissue and which exert pressure

The most common cause of failure to accommodate to increased barometric pressure is infection of the upper part of the respiratory tract with the result that swollen lymphoid and other tissue acts to seal the openings of the auditory tubes and less frequently the sinal meatuses With reference to the ear the pain may be felt over the mastoid area as well as in the auditory canal indicating that the entire membranous lining of the middle ear and mastoid cells is involved The varying degrees of barotrauma in the middle ear may be observed by otoscopic examination of the tympanic membrane to reveal (1) injection of the membrane (2) injection with hemorrhage (3) gross hemorrhage and free fluid in the middle ear (4) rupture of the membrane which requires a difference in pressure of the order of 250 to 500 mm Hg Complications of suppurative *otitis media* moreover are infrequent if the traumatized tissues do not come in contact with contaminated water Spread of infection from the nasopharynx by air passing into the auditory tubes during compression is not established

Effect on Hearing Following acute trauma the audiogram reflects diminished perception of sound over the whole frequency range As the pathologic condition undergoes resolution hearing returns usually to the initial level of acuity This absence or rarity of proved cases of deafness from barotrauma stands in contrast to the permanent deafness from gun fire injury

Overdistention of the Lungs (Traumatic Air Embolism) Ascents have been made routinely in submarine escape training tanks from depths of 100 ft During such ascents the compressed gas in the lungs and in the breathing bag escapes through a relief flutter valve such that intrapulmonic pressure is permitted to approximate the ambient hydrostatic pressure If the individual, however holds his breath during ascent the intrapulmonic pressure will become greater than the hydrostatic pressure and will overdistend the lungs rupturing alveolar sacs and blood vessels Gas thus may be forced or aspirated into the blood stream giving rise to symptoms referable to the circulatory and central nervous systems

Spontaneous Pneumothorax During rapid decompression either with or without air embolism *spontaneous pneumothorax may* occur in the distended lung

Overdistention of Abdominal Viscera In ascent from deep diving depths the expansion of gas previously swallowed under pressure in the stomach and segments of the large bowel is a restraint to further decompression A viscus once having been distended by gas appears to lose much of its propulsive motility In distention of the stomach for example the cardiac and pyloric sphincters become spastic and prevent elimination of gas

SECONDARY PRESSURE PHENOMENA INDUCED BY INCREASED GAS PRESSURES

The phenomena previously described have arisen primarily from differences in pressure which have acted to distend and rupture blood vessels and membranes lining closed spaces On a wholly different basis are those pressure phenomena associated with disturbances in gaseous equilibriums

Narcotic Action of Nitrogen When the air pressure is raised to 4 atm or higher gaseous N induces a narcotic effect shown by decreased neuromuscular coordination and changes in mood frequently euphoria The responses are similar to those associated with hypoxia or alcoholic intoxication Although all individuals are to some extent narcotized at deep diving depths stable individuals apparently react to the stress by increased volitional effort and carry out their tasks until consciousness is lost The unstable individual on the other hand is incapable of purposeful effort

The substitution of helium for N diminishes the narcotic effect of high air pressures In contrast with aquatic animals however symptoms attributable to high partial pressure of gases may completely incapacitate the individual

It is of interest that rare gases such as xenon which are chemically inert are nevertheless capable of producing surgical anesthesia when administered

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106 DISORDERS DUE TO ALTERATIONS IN BAROMETRIC PRESSURE

Albert R Behnke

These disorders although of prime military interest are also of direct concern to physicians *dealing with problems arising from air transport* residence at high altitudes or tunnel operations In recent years increased participation in skin diving (i e with self contained breathing apparatus) constitutes a further hazard to several million young persons With increased knowledge of the action of environmental (ambient) oxygen (O) particularly as a regulator of hematopoiesis and its utilization at normal and increased pressure with the realization that one of the toxic manifestations of O administered to premature infants is retrolental fibroplasia with the need to utilize in experimental work various gases under controlled conditions of temperature and pressure with the breakdown of the distinction between civilian and military in defense problems and finally with the knowledge that nascent gas bubbles (in contrast with gas accidentally aspirated into the veins) simulate a variety of pathologic states there is need for the physician to be cognizant of the physiologic changes associated with alterations of barometric pressure

PRIMARY PRESSURE PHENOMENA

Hydrostatic and Gaseous Pressure Adaptations in Aquatic Animals That pressure itself is without injurious effect to life is evident from the fact that aquatic animals exist in a pressure environment of 100 atmospheres (atm) or more Similarly if care is taken not to injure the swim bladder by rapid decompression, greatly increased water pressures will not impair the marine organism The diving mammals illustrate particularly this facile adjustment to pressure alterations A point of further interest in connection with aquatic animals is the *clear cut separation between the effect of the hydrostatic forces per se* and the action of partial pressures of gases Moreover in the swim bladder of the fish one is confronted with the amazing phenomenon that the pressure of gases such as N and O may be many atmospheres higher than the partial pressure of these gases within the tissues of the fish

Effects of Pressure Applied Equally to All Parts of the Human Body Divers have been compressed to almost 18 atm (equivalent to a diving depth of almost 550 ft) without demonstrable damage from the compressive force itself provided that air has free access to all surfaces of the body e g the membranous linings of the middle ear mastoid air cells frontal and ethmoidal sinuses In this connection it should be noted that although the absolute cerebrospinal and blood pressures are increased by 18 atm the manometer recordings of these pressures may not be altered by as much as 1 mm Hg Therefore in so far as the pressure forces operate the brain is not in a "closed box" but is subject to the same compressive forces as *is the skin Similarly a decrease in ambient air* pressure to 0 12 atm (equivalent to an altitude of about 55 000 ft) will not in itself cause injury

Only equal distribution of pressure however preserves unaltered the structure of tissues and the body as a whole

Effect of Unequal Pressure Application (Barotrauma) If the pressure is not equally distributed over all body surfaces a pressure difference between the ambient atmosphere and tissues of more than about 50 mm Hg [1 lb per sq in (psi)] will distort tissue and induce congestion edema hemorrhage and pain *Barotrauma produces a condition* known as squeeze A pearl diver for example is subjected to an additional compressive force of 1 atm for every 33 ft of depth and at 100 ft the total pressure acting on his body is of the order of 4 atm The air in the divers chest at the surface (approximately 6 000 ml) is compressed at this depth to one fourth the surface volume or 1 500 ml (the normal residual air volume') Should the diver descend deeper hydrostatic pressure acting

hypothermia the O_2 in physical solution when pure O_2 is inhaled will meet tissue requirements without the need for hemoglobin as an O_2 carrier These and other similar investigations should greatly extend the scope of O_2 therapy in the treatment of acute critical conditions if facilities become available

Effect on Erythropoiesis It has been shown by Tinsley et al that O_2 breathed by normal persons in concentrations of 50 to 70 per cent (0 5 to 0 7 atm) depresses erythropoiesis (decreased utilization of radioactive iron) in patients with chronic hemolytic anemias pernicious anemia and sickle cell anemia In the last condition the highly active bone marrow is particularly responsive to the depressive effect of the raised O_2 pressure This topic will be developed further in connection with comments on the effect of low O_2 pressures

Fire Hazard The imminent danger of incineration when O_2 is employed makes mandatory meticulous precautions in handling

Carbon Dioxide The augmented cerebral blood flow in the presence of increased alveolar and blood CO_2 tensions explains in large measure the enhanced toxic action of inhaled O_2–CO_2 mixtures and also the enhanced narcotic action of N_2 during the tissue uptake period Indeed the cerebral vasodilatation and increased blood flow associated with the inhalation of atmospheres rich in CO_2 increases the effect of any ambient gas pressure

Tolerance to High Concentrations For submarine operations increased partial pressure of CO_2 in air is considered to be 21 mm Hg for periods not longer than 72 hr Individuals in good physical condition may be exposed to a partial pressure of 36 mm Hg (5 per cent) for periods up to 60 hr This is an upper limit which may be lower for men in a state of chronic fatigue Schaefer has reported evidence of central nervous system depression following the prolonged inhalation (several days) of 2 to 3 per cent CO_2–air mixtures There are so many physiologic variables in the CO_2-tolerance problem that generalizations cannot be made However toxic symptoms attributable to CO_2 are at the low level of injury and appear to be readily reversible There have been no truly long experiments (several months duration) to indicate whether or not real acclimatization to the high CO_2 environment takes place e g the decreased sensitivity to high concentrations of CO_2 mirroring the greater sensitivity to CO_2 observed in residents at high altitude

DECOMPRESSION SICKNESS

Of all the debilities incident to abnormal pressure environments those pertaining to rapid decompression of divers and caisson workers or in the case of the aviator change from normal pressure to substratospheric altitudes are perhaps the most dramatic All persons under these conditions are exposed to acute and possibly chronic injury from nascent gas bubbles principally from those forming in the blood stream and producing intravascular shutting off of circulation to and within important organs Without recompression which forces the free gas into re solution death supervenes within a matter of minutes

Not only are the injuries characteristic of decompression sickness of intrinsic interest but they also simulate a variety of clinical conditions e g shock arteriosclerosis of the terminal aorta involving lumbar segmental arteries and tabes dorsalis Even infection with its pain weakness malaise fever and sweating may be simulated by this condition The nascent gas bubble is replacing the spirochete as the "Great Imitator

A comprehensive monograph on the subject has been assembled by the National Research Council (John Fulton) There is also a recent publication on submarine medical practice prepared by the U S Navy as well as a comprehensive report of proceedings "Underwater Physiology Symposium published by the National Research Council

Death from decompression sickness has been reported following rapid ascent to high altitude in jet aircraft Likewise injury to the spinal cord incident to altitude decompression heretofore considered rare or nonexistent has been described by Haymaker

Regional signs and symptoms of decompression sickness may be tabulated as follows

Table 88 REGIONAL SIGNS AND SYMPTOMS OF DECOMPRESSION SICKNESS

Central nervous system	Cardio-respiratory system	Extremities	Skin
Hemiplegia	Substernal distress	Pain (bends)	Pruritus
Spastic mono- or paraplegia	Paroxysmal coughing on deep inspiration	Numbness	Mottling
Hyperesthesia	Shallow rapid respiration	Weakness	Rash
Anesthesia	Asphyxia	Infarction of bones	Pallor cold sweating
Scotoma	Shock		
Diplopia	Circulatory insufficiency		
Ménière's syndrome			

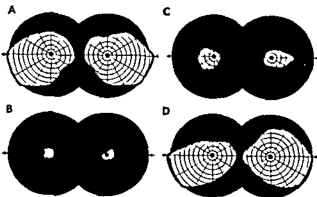


Fig 136 Perimetric measurements made before and after inhalation (3 5 hr) of oxygen at 3 atm pressure (*Behnke et al Am J Physiol* 114 436 1935)

in high concentrations at normal barometric pressure

Oxygen *Toxic Effects* Since the time of Paul Bert it has been known that O induces convulsive seizures in lower animals at pressures of 4 atm or higher Oxygen inhalation by man at the same pressure produces syncope in some individuals and seizures in others Electroencephalographic tracings taken under these conditions may be similar to those found in epileptic patients

At 3 atm pressure seizures do not usually occur The inhalation of O may be well tolerated by healthy adults for a period of several hours During the fourth hour of O inhalation there may occur a rise in blood pressure increase in pulse rate extreme pallor and periodic waves of nausea Of particular interest and further evidence of the intense generalized vasoconstriction is contraction of the fields of vision terminating in amblyopia followed by recovery when air is again inhaled (Fig 136) This is of interest in connection with retrolental fibroplasia experimentally produced in lower immature animals exposed to high concentrations of O It follows that the concentration of O administered to premature infants must be limited to a tension of 300 mm Hg (about 40 per cent of 1 atm approximately 20 per cent less than the generally accepted safe level of 60 per cent given to adults) in order to provide a wide margin of safety

Following prolonged exposure (4 to 6 weeks) to O pressures of 0 7 to 1 atm there may develop in rats pulmonary arteriolar lesions (thickening and hyalinization leading to thrombosis) and later degenerative lesions of the large arteries of the lungs Pertinent is the fact that the obliterative vascular changes are followed by a rise in pulmonary pressure enlargement of the right ventricle and a fall in systemic blood pressure Similar findings occur in man at high altitudes when there is a "break in adaptation" i e loss of ability to work at high altitude Such inability is associated with obliterative endarteritis pulmonary hypertension (Ayerza s disease) and a secondary erythrocytosis superimposed upon the normal adaptive red blood cell (RBC) response to lowered *p*O (Monge)

Procedures or Substances Which Increase Oxygen Toxicity Exercise markedly lowers the tolerance time for the inhalation of O Thus seizures have been reported at diving depths of 33 ft (+2 atm abs) in contrast to a tolerance time of some 10 to 30 min when O is inhaled by individuals at rest in a pressure chamber i e simulated depth of 100 ft (+4 atm abs) Carbon dioxide added to O also greatly increases its toxicity Disturbed transport of CO when O is inhaled at high pressure does not now appear to be a primary factor The exercise and CO effects may be interrelated The individual response to O inhalation in view of such factors as CO and exercise is understandably highly variable Specific note should be taken of the altered sensitivity of the respiratory centers to CO when O is inhaled

Procedures or Substances Which Decrease Oxygen Toxicity From the investigations of Gerschman Bean and others it is now evident that the following procedures or substances diminish the toxic effects of O at high pressures hypophysectomy thyroidectomy adrenalectomy drug depression of metabolism hypothermia lowered alveolar CO tension —SH compounds and bivalent metals i e Mn Co Mg and C Of special interest are data of Gerschman to support certain radiomimetic effects of O at high pressure

Tolerance to Oxygen Pure O at atmospheric pressure produces substernal soreness It is the partial pressure and not the percentage of O that is important for when the pressure is lowered to 0 25 atm equivalent to 34 000 ft it is possible to continue the O inhalation without symptoms In man (adults) and in lower animals all data agree that O pressures of 400 mm Hg or less (about 60 per cent of 1 atm) are not toxic

Therapeutic and Experimental Employment of Oxygen at Pressures above 1 Atm About 2 ml of O is dissolved in 100 ml blood At 3 atm pressure inhalation of O makes possible a supply of O in solution to tissues without the need for reduction of HbO In the treatment of acute CO poisoning J B S Haldane Pace and others have proved the rationale of utilizing O in pressure chambers by hastening the dissociation of HbCO in the presence of an ample supply of O to tissues

In experiments on animals Brauer has observed beneficial effects of high O in rats whose livers would have been otherwise irreversibly damaged by carbon tetrachloride Furthermore he has eliminated the need for red blood cells as O carriers in the perfusate employed in the isolated rat liver preparation

At atmospheric pressure under conditions of

PHYSIOLOGIC CONSIDERATIONS AND DERANGEMENTS AT HIGH ALTITUDES

Maximal Performance of Partially Acclimatized Individuals (1 to 3 Months) The successful scaling of Mt Everest (29 002 ft) by a British Sherpa expedition in 1953 has been repeated by a Swiss expedition Also three other expeditions have been successful in scaling previously inaccessible peaks in the 26 000 to 28 000 ft range In the K2 (28 250 ft) Italian expedition (Desio) O_2 was used initially but not in the final stage of the climb or the return In the French expedition (Herzog) to the top of Annapurna (26 503 ft) and the German Austrian expedition (Buhl) to the summit of Nanga Parbat (26 660 ft) O_2 was not employed These feats which entail severe hypoxia hypocarbia extreme cold inordinate muscular effort disturbed alimentation and stress reactions to danger represent an ultimate in human endurance Members of mountain climbing expeditions who are not native inhabitants of an area between 14 000 and 18 000 ft altitude may be only partially acclimatized during the usual training period of 1 to 3 months at these terrains Above 18 000 to 20 000 ft there is a critical level or true ceiling above which no further adaptation and acclimatization are possible Natives to the 14 000 ft terrain do not appear to be superior to the recently acclimatized (3 to 4 weeks) mountaineer at altitudes above 23 000 ft Above 25 000 ft (the "death zone") rapid deterioration of the physical and mental state takes place if O_2 is not used hence mountain climbers have only about 10 days at or above this altitude to accomplish their objective

Functional and Morphologic Characteristics of the Native Resident at High Altitude A comprehensive comparison between the native resident of Morococha Peru (14 900 ft) and the native living in Lima (sea level) has been prepared by Hurtado and his coworkers Important differences which characterize the Andean as contrasted with the dweller at sea level (SL) are (1) decreased body weight (5 kg) relative to stature and increased vital capacity (2) increased pulmonary ventilation amounting to about 30 per cent per liter of O_2 consumed (3) decreased alveolar pCO_2 (29 mm Hg SL 39 mm Hg) (4) a greatly diminished O_2 pressure gradient and decreased HbO_2 saturation as shown in Table 90 (5) a lowered blood bicarbonate level proportionate to the fall in alveolar CO_2 such that the pH of the blood of the Andean is within normal limits (6) an increase in hemoglobin (21 Gm SL 16 Gm) and O_2 carrying capacity of blood (despite the low alveolar pO_2) amounting to about 1 9 vol per 100 ml (7) an increase in blood volume of about 20 per cent and (8) an increased size of the capillary bed specifically in brain tissue as demonstrated by Schneider

Table 90 EFFECT OF OXYGEN PRESSURE ON HbO_2 SATURATION

Altitude	Oxygen pressure mm Hg			Per cent HbO_2 saturation
	Tracheal	Alveolar	Capillary	
15 000 ft	84	53	41	80
Sea level	147	99	62	98

Table 91 EFFECT OF OXYGEN PRESSURE ON RED BLOOD CELLS

Ambient O_2 atm	Rabbit 1		Rabbit 2	
	Exposure days	RBC million/cu mm	Exposure days	RBC million/cu mm
0 6	28	3 0	20	3 0
0 4			18	4 2
Normal 0 2	108	5 5	56	6 0
0 1	33	9 0		7 7

Specific Erythropoietic Effect of Low Ambient Oxygen Pressure The quantification of response of erythroid elements to variation in O_2 is exemplified in Campbell's (1926) classic experiments In rabbits exposed in stages to a fivefold variation of either high to low or low to high oxygen pressure there occurred a corresponding change in red blood cells of about 250 to 300 per cent as shown in Table 91

Thus it appears that the ambient pO_2 and in turn tissue pO_2 constitute one of the principal regulators of the level of erythropoiesis The role of the bone marrow pO_2 in this matter is not established

Ability to Work The native at high altitudes performs work more efficiently than the resident at sea level in terms of O_2 consumption per unit of weight blood lactate level O_2 debt and pulse rate Irrespective of the reason for the increased efficiency of the native at a high altitude (perhaps because of less excess fat and better physical condition) he is at least as well adapted to his environment as is the resident at sea level

Summary of Functional Changes Making for Acclimatization (from Hurtado et al) From the consideration of the comparative observations presented it is obvious that the permanent resident

Table 89 REPRESENTATIVE BLOOD PRESSURE RESPIRATORY RATE AND BLOOD FINDINGS OF AN ANESTHETIZED DOG RAPIDLY DECOMPRESSED AND SUBSEQUENTLY RECOMPRESSED IN A HIGH PRESSURE CHAMBER

	BP mm Hg	RR No /min	O_2 content vol %		AV diff vol %	O_2 cap vol %	% HbO		Art CO_2 tension mm Hg
			Art ‡	Ven §			Art	Ven	
Control	132	20	15 9	10 1	5 8	17 7	90	57	45
Postdecompression *	80	134	5 4	0 5	4 9	22 4	24	2	59
Recompression †	90	32	17 9	7 9	10 0	20 3	88	39	
Postrecompression	114	140	5 9	2 3	3 6	22 8	26	10	

* From 65 lb gauge (5 3 atm abs)
† 30 lb gauge (3 atm abs)
‡ Blood withdrawn from femoral artery
§ Blood withdrawn from right atrium
SOURCE Behnke et al Am J Physiol 114 526 1935

Specific comments will be made only with reference to the cardiorespiratory manifestations and bone lesions

Cardiorespiratory Symptoms and Signs The earliest symptom indicative of bubbles in pulmonary vessels following decompression is a sensation of substernal soreness on deep inspiration which elicits paroxysmal coughing (Behnke) When intrapulmonic bubbles increase sufficiently in number rapid shallow breathing (tachypnea) supervenes (Table 88) In the starch experiments of Binger et al shallow rapid respiration (rate 100) was also observed when appreciable quantities of starch were injected Small numbers of gas or starch emboli have been found to have no effect on respiratory rate

With reference to blood gases and HbO saturation the effect of the embolic obstruction in pulmonary vessels is manifest by increased AV difference hemoconcentration and a remarkably low desaturation of hemoglobin (Table 89)

Bone Lesions The osseous and arthritic lesions are always chronic They are painless and insidious when only the shafts of the bones are involved and are identified as sequelae of decompression in caisson workers *mainly on the basis of occupational* history Because of the industrial compensation problem there has been considerable interest in these lesions and a number of excellent reports (e g Taylor Poppel and Robinson) have appeared

The underlying morphologic change is essentially aseptic necrosis due to the obliteration of the blood supply in the diaphyseal portions of the shafts of long bones or in the subchondral portions of the articular surfaces It is the shaft lesions which are usually asymptomatic The joint lesions may be painful and secondary arthritic changes may develop and present an appearance similar to that of chronic osteoarthritis

Types of Injury in Connection with Skin Diving and the Use of Self-contained Breathing Apparatus This subject is treated in detail in appropriate manuals e g Bureau of Naval Personnel Manual on Submarine Medical Practice Because of the wide participation in this sport by adolescents and young adults the following accidents or conditions which already have resulted in fatalities are enumerated (1) drowning as a result of defective equipment (2) air embolism (overdistention of the lungs) (3) barotrauma (injury to ears sinuses and severe hemorrhagic injury to the eyes due to loss of mask pressure) (4) overexertion hypoxia CO excess N narcosis O_2 toxicity CO poisoning (when compressed air is employed) hypothermia and decompression sickness

Treatment of Decompression Sickness The objectives in treatment are immediate and extended recompression even of several days duration and the judicious employment of O and fluids Such therapy has brought about recovery of divers seemingly *in extremis* To treat the shock syndrome *resulting from too rapid ascent more pressure than* that at ground level may be required The most frequent errors in treatment of decompression sickness are

1 Failure to give treatment to doubtful cases

2 Delayed recompression The longer treatment is postponed the more pressure will have to be applied

3 Failure to treat the serious cases adequately

4 Failure to keep the treated patient near the chamber for a 24 hr period

The watch officers bunk was too small to permit one to lie on his back One was forced to lie on one side and then being wedged in between the bulkhead to the right and the clothes-press on the left to hold fast against the movements of the boat underway Cooking was done on the deck using a gasoline stove gasoline engines propelled the boats and consequently poisoning from gasoline fumes was common One awoke in the morning with considerable mucous in the head and frequently with the so-called oil head" Living in a submarine was like living in a damp cellar since moisture inside the submarine condensed on the steel hull plates which were cooled by the sea water (1912)

The interior of the atomic submarine is pleasant and comfortable Air conditioning special lighting color schemes and interior design conducive to eye comfort and esthetic satisfaction are incorporated into the general plan Comfortable berthing and messing spaces are provided along with toilet and even bathing facilities The recreational outlay includes a library tables for small games a motion picture projector and phonographs! (1956)

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107 RADIATION INJURY

Shields Warren

EFFECTS OF SUN AND ULTRAVIOLET LIGHT

Injury from sunburn is probably the most wide-spread to which the human race is subject Sunburn commonly does not go beyond erythema sometimes accompanied by slight swelling of the affected skin and is followed in the course of days or weeks by hyperpigmentation Rarely is sunburn sufficiently severe to produce second degree burns although moderate first-degree burns are not infrequent Systemic reactions are usually slight although in more severe cases there may be fever and transient leukocytosis Ultraviolet light may produce sunburn The cornea is particularly sensitive to ultraviolet light and even a brief exposure may lead to keratitis and conjunctivitis Years of continuous exposure to insolation or ultraviolet light leads in other than very heavily pigmented skins to increased incidence of carcinoma either epidermoid or basal cell in type

at high altitudes has certain definite respiratory characteristics which may be interpreted as adaptive mechanism to the hypoxic condition resulting from the low environmental pressure Hyperventilation is one of these characteristics The main favorable effect of this process is a rise in the alveolar pO_2 which is accompanied by a decrease in the alveolar pCO_2 It is also possible that a more uniform ventilation takes place at high altitudes

The hematologic aspects of natural acclimatization to high altitudes are characterized mainly by a polycythemia of an absolute type which is the consequence of an increased rate of activity in the formation of red blood cells and hemoglobin in turn this is associated with a proportional accentuation of the processes related to red cell destruction The equilibrium between production and destruction are maintained at a higher level From the early days of high altitude investigation it has been accepted that the hypoxia in this environment is the stimulating factor responsible for the increased hematopoietic activity which affects only erythroid cells Recently a renewed interest has been placed in the study of the humoral control of erythropoiesis by substances of pituitary hepatic and splenic origin

Of the possible adverse effects of altitude residence mention may be made of increased pressure in the pulmonary artery with enlargement of the right ventricle These changes may develop into the decompensatory derangements of frank pulmonary hypertension and cor pulmonale of Monge s disease By contrast high blood pressure and coronary thrombosis are rarely observed

Acute Exposure to Hypoxia In contrast with the native resident the newcomer to an altitude of 15 000 ft does not have the capacity for work His immediate adjustments are primarily respiratory and circulatory since time is required to effect somatic changes Respiratory alkalosis and disturbed sleep are well recognized phenomena during this initial period The most striking findings however relate to glandular changes and altered glandular function which are accentuated in lower animals subjected admittedly to a severe condition of hypoxia These changes may be enumerated as follows

1 Enlargement principally of the adrenal cortex
2 Increased secretion of epinephrine
3 Increase in blood sugar
4 Decrease in thyroid function equivalent to that resulting from thyroidectomy
5 Decreased gastric motility
6 Loss of fertility degeneration of spermatogenic cells
7 Hemorrhages in the intestines and other organs

Although certain blood changes with reference to hemoglobin content and acid base balance have been studied in detail there remain gaps in the knowledge of the fundamental mechanisms involved when acute compensatory reactions fail Excellent reviews of the present state of knowledge are to be found in the studies of Dill Hurtado et al Van Liere and Monge Aviation medical problems are analyzed in the standard reference books by Armstrong and by McFarland

Chronic Mountain Sickness (Monge s Disease) This disease is manifest by the appearance of vascular congestion and cyanosis impaired ability to work, and the following specific derangements using the values of the healthy native resident at altitude as standard (N) Hemoglobin 25 Gm per 100 ml N 21 Gm per 100 ml (blood hematocrit 80 per cent N 60 per cent) There are a blood volume increase of about 50 per cent hyperplasia and hyperactivity of bone marrow erythroid cells abnormal red blood cell destruction relative *hypoventilation* increased cardiac output electrocardiographic findings consistent with the diagnosis of cor pulmonale and associated with a greater pulmonary hypertension and a lower systemic blood pressure than found in the healthy resident

The symptoms and signs of Monge s disease have much in common with Ayerza s syndrome (erythremia cyanosis dyspnea hyperplasia of bone marrow and sclerosis of the pulmonary artery) which apparently has a multiple etiology and with the findings (pulmonary injury and hypertension) following exposure to elevated O_2 pressure referred to in an earlier section

CONCLUDING NOTES

The author desires to emphasize the necessity for frequent physical examination of individuals engaged in hazardous activities who are subject to impairment from physical agents It is mandatory for example *to examine deep sea divers daily* For this purpose a permanent record of pulse rate (counted for 1 min) and blood pressure taken daily prior to the work of the day usually suffices as a control base line in the evaluation of any given individual Deviation of more than ±35 per cent from the mean recorded values requires extended examination This procedure has prevented disability and fatal accidents

Finally in combating the adverse effects of physical agents or a foreign atmospheric environment it is well to realize that a cooperative engineer is the doctor s best friend To illustrate this point let us compare habitability in a German submarine as reported by an officer in 1912 with living conditions in a present day atomic submarine

O ernight crui es were avoided since they were not only considered highly uncomfortable but unhealthy

The dose of external ionizing radiation delivered within a short period of time required to kill half a given human population is about 400 r However if the region of radiation is restricted to a fraction of the body as in the treatment of cancer several times this dose can be given without appreciable systemic effect and with only localized destruction of cells

While in general the radiation of localized tumor bearing portions of the body can be accomplished without serious harm to the rest of the body there may be minor systemic reactions These reactions have been termed *radiation sickness* in the past and are probably due to absorption of protein split products from damaged tissues The patient may react with anorexia nausea and rarely vomiting these are usually transient and without significant organic change

If the intestines or a portion of them are included in the field of radiation and that radiation is heavy (5 000 r or more such as might be used in treatment of carcinoma of the cervix) there may be some diarrhea due to acute injury of the intestinal mucosa Later there may be partial obstruction resulting from scarring and fibrosis with or without ulceration If the liver is included in any field of radiation receiving above 1 500 r the chance of radiation sickness is increased There are usually no significant alterations in the various components of the body fluids during this sequence of events although a transient increase in amino acid excretion in the urine may occur This type of radiation sickness due to local therapy should not be confused with the acute radiation syndrome which is the result of irradiation of much or all of the body

In sharp contrast to the relatively minor reactions encountered as a result of therapeutic radiation of a portion of the body are the effects of the irradiation of the entire body as for example in a nuclear reactor accident or the explosion of an atomic bomb

The acute radiation syndrome is quite different from the effects of chronic low level radiation on the body although the late results of acute whole body radiation may be quite similar to those of chronic exposure Four phases have been described but they are not constant the acute onset with malaise ranging up to prostration usually lasting some hours a phase of relative well being lasting up to several days a period of severe illness of varying character and duration finally recovery or death Fever may develop early and particularly in the absence of infection is an unfavorable sign

In total body radiation the relative sensitivity of the different body tissues largely determines the clinical character of the response If the radiation is sufficiently overwhelming to damage most cells without regard to their relative susceptibility to injury death usually occurs within a matter of hours or days with no distinctive symptoms or signs other than weakness and lassitude progressing to prostration accompanied by a marked leukopenia More usually however the dose of radiation is not sufficiently great to be immediately lethal so that there is opportunity for the varied sensitivity of the different systems of the body to become apparent

Probably the most sensitive cells of the body are the lymphocytes The precursors of the granulocytes are quite sensitive also so that a leukopenia usually develops within 24 hr after exposure following a transient leukocytosis of 12 000 to 20 000 cells per cubic millimeter The prominence and degree of the leukopenia are roughly proportionate to the degree of exposure and hence are of some prognostic value If the white cell count falls below 2 000 per cubic millimeter within the first few days following exposure recovery is unlikely Owing to the longer life of the red blood corpuscles anemia develops more slowly in spite of the great sensitivity of the erythroblasts but may be severe

Hemorrhagic manifestations referable to the combined effect of thrombocytopenia induced by the radiation increased capillary permeability from damage to the endothelial cells and alterations in the coagulability of the blood probably largely mediated through hepatic damage are of importance In the survivors at Hiroshima and Nagasaki hemorrhages both internal and from body orifices petechiae and ecchymoses reached their peak 5 to 6 weeks after the initial exposure The symptoms and signs due to them are variable depending on the location and extent of the hemorrhage

A severe anemia frequently accompanied by pancytopenia develops after several weeks This is not because of resistance of the erythropoietic tissue itself which is highly sensitive but rather because of the long life of the circulating erythrocytes which delays evidence of the damage to the parent tissue The bone marrow during this stage may show aplasia or hypoplasia in which case the outlook for ultimate recovery is not too good or it may show hyperplasia with delayed maturation

Regeneration may be effective and complete or it may be partial In some instances there is apparent failure of maturation large numbers of young forms proliferating and even crowding the marrow for months afterward

Not only is the leukopenia an evidence of serious damage to the body as a whole but also its existence permits infection to become established Multiple cutaneous abscesses stomatitis and cellu

EFFECTS OF IONIZING RADIATION

All living matter is continuously exposed to minute amounts of ionizing radiation derived from both cosmic radiation and the traces of naturally radioactive materials in the soil and water chiefly isotopic potassium and radium These minute amounts constitute the so called background radiation which is of such low intensity that it exerts no significant effect and rarely integrates to more than 20 r in a lifetime

The r or roentgen is an arbitrary unit based on ionization of air The term *rep* roentgen equivalent physical is used to designate the roentgen as determined by instrumentation it is that quantity of ionizing radiation that yields 93 ergs per Gm as it undergoes absorption in tissue The term *rem* roentgen equivalent man is used to designate the quantity of ionizing radiation which produces an effect in man equivalent to that produced by absorption of 1 r of hard x ray radiation

The Committee of the National Academy of Sciences on the Biological Effects of Atomic Radiation estimates that in any 30 years (by which time parents in the United States have conceived over half their children) the dose of background radiation is 4 to 5 5 r According to their estimates the average accumulated dose to the gonads from medical x rays is about 3 r during the same period The radioactive fall out from weapons testing continued at the present rate is estimated to produce a 30 year dose of about 0 1 r

The permissible level of occupational exposure to radiation set by the International Committee on Radiation Protection is 0 3 r per week However very few persons engaged in radiation or atomic energy work approach this level As a further precaution geneticists have recommended that the total dose received by the gonads of even occupational workers not exceed 50 r prior to age thirty

Exposure to significant amounts of radiation does not occur naturally Radiation may be external as from an x ray tube or internal as from radium poisoning or the administration of radioisotopes such as iodine^{131}

Since ionizing radiation cannot be detected by the senses and since its effects are not immediately apparent special precautions must be taken to protect against it when its presence is known or suspected The chief means of monitoring are photographic film electroscopes and Geiger counters Scintillation counters are of value in special cases

Although there are four general types of ionizing radiation—alpha particles beta particles gamma rays and neutrons—they vary greatly in their biologic effectiveness but their qualitative effects on living cells are similar Along the path of an alpha particle ionization is much denser than along that of a gamma ray while its penetration in tissue is much less than that of the gamma ray As a general rule the more penetrating the radiation the less is absorbed by any given unit of tissue and hence the less the biologic effect This variation in effect is known as RBE relative biologic effectiveness" The response of cells to injury by ionizing radiation does not vary qualitatively with the type of radiation but signs and symptoms vary with the amount of tissue damaged and its location

The *mechanism of action* of ionizing irradiation on protoplasm has not yet been sharply defined That ion pairs are formed is clear and that they may disrupt protein molecules and intracellular enzyme systems is also established The effect is so great as compared to the energy released that one has to assume that multiplication of the injury must occur as in an enzyme system

That hydrogen peroxide or oxidative radicals from water are formed within the tissues or that heat is developed due to localized absorption of energy—these are two among the hypotheses that have been put forward to explain radiation changes

The effect of radiation depends to a considerable degree on the rate at which the radiation is given and on the volume of tissue irradiated In general microorganisms or relatively unorganized cells such as those growing in tissue culture are much more resistant to radiation than are more complex organisms

Shorter lived and hence more rapidly proliferating cells are generally rather more sensitive to radiation than are cells with little or no proliferative activity Thus a granulocyte with a life of 3 or 4 days is far more sensitive than is a cortical pyramidal cell with a life approximately that of the individual in whom it exists Cells in mitosis are much more sensitive to irradiation injury than are resting cells

Experience has shown that human somatic cells are not injured by radiation of very low intensity owing to their regenerative powers While only scattered data exist concerning effects on human germ cells and animal experiments have not yet been conclusive it appears that moderate amounts of radiation are required to produce significant genetic mutations On these bases the level of permissible occupational exposure of the entire body has been set at 0 3 r per week which provides a reasonable factor of safety A single dose of 25 r will cause no significant injury though changes in circulating lymphocytes can be brought about by doses as low as 15 r Some degree of illness is almost constantly produced by a dose of 150 r delivered to the entire body The life span will probably be shortened by a dose of 75 r

have followed the use of relatively large amounts of radioactive iodine In man I^{131} has not induced thyroid tumors even though some of the therapeutic levels have been fairly high However among the thousands of cases treated thus far four cases of leukemia have subsequently developed which exceeds the expected incidence

There is evidence from animal experiments of a shortening of the life span as a result of chronic low level radiation premature aging and lowered resistance to infection seem to play a part in this phenomenon

There is evidence that the accumulation of 1 000 r more or less of total body or nearly total body radiation will shorten the life span in man about 10 per cent

A new source of chronic low level radiation has been added by the advent of atomic energy However such great care has been taken in the use of it so far that the radioactive fall out either from weapons tests or from atomic energy installations is relatively insignificant Radioactive strontium is the chief element for concern in fall-out since its long half life (25 years) its chemical similarity to calcium and its ready uptake by both plants and animals make it the single most dangerous component Radioactive fall out has been distributed by now all over the world by the stratospheric winds and slow settling throughout the atmosphere However if the present level of activity of nuclear testing is continued for about 30 years the average dose to the gonads of the population for that period would be on the order of 0 1 r only and hence negligible Although radioactive strontium has been found in human bone and in various animal tissues it has been well below dangerous levels

Medical Effects of the Atomic Bomb Since the possibility of atomic warfare makes it necessary that every physician be familiar with the general principles of injuries resulting from an atomic explosion some mention will be made of blast and thermal injuries as well as of those due to ionizing radiation even though the former are not strictly within the field of internal medicine

The burst of an atomic bomb in air has been compared to an explosion of 20 000 tons of TNT which releases in addition to mechanical energy an enormous amount of radiant energy in the form of infrared visible and x ray radiation as well as a flux of neutrons In an air burst residual radiation from radioactive fission products of the bomb is not a major problem as very little of the fission products reach the ground at the site of explosion but rather are swept up into the stratosphere where they are greatly dispersed and do not achieve a significant concentration when fall-out occurs

In an underwater burst on the other hand as in the second Bikini test residual ionizing radiation may be a very serious problem not only is there temporary radioactivity in the components of the water from the effects of the neutron flux but in addition the radioactive fission products are mixed in the column of water and cloud resulting from the explosion and are rained back upon whatever is beneath However air blast and thermal radiation are not significant

In an air burst secondary air blast injuries resulting from falling structures and flying debris are frequent and varied and range from severe crush to minor lacerations On the basis of Japanese experience crush injuries will predominate with a high incidence of less significant but painful and disabling accidents from flying glass fragments Primary air blast injuries may be largely discounted Any person sufficiently close to the center of an atomic explosion in air to have received primary air blast injury would have received also a lethal dose of ionizing radiation and probably would be fatally burned in addition

The burns received from the thermal energy liberated are of two types flash burns and flame burns Flash burns result from the direct heat of the bomb explosion itself The burns are sharply demarcated and usually restricted to exposed areas of the skin varying in intensity from severe to slight according to the distance from the point of explosion In Nagasaki some flash burns developed in persons up to 2 miles from the hypocenter Flame burns are due to the fires incident to the explosion of the bomb and are in no way different from those commonly encountered Both these types of burns should be treated as comparable burns from non atomic sources would be treated

The ionizing radiation received from the bomb burst is almost instantaneous in character and as already stated a dose of 400 r over the total surface of the body is sufficient to cause death of about half the exposed population

The first symptoms to appear are nausea and vomiting shortly followed by diarrhea Fever accompanies the more severe cases Those receiving heavier doses of radiation (1 200 r or above) will die within 1 to 30 days in spite of treatment

In the cases that survive the first few days signs and symptoms referable to effects upon the more sensitive tissues of the body will be more clearly defined Phagedenic ulcers and septicemia may develop as a result of the destruction of white blood cells and their precursors About this same time or up until 6 weeks later hemorrhagic manifestations appear they are due to damage to megakaryocytes interference with the heparin antiheparin balance of the blood and increased capillary permeability

In some of those surviving beyond 6 weeks a gradually developing pancytopenia appears which eventually leads to death Bone marrow biopsy may

litis of the neck are among the more obvious developments The pathogenic agents may be a wide variety of organisms including those usually saprophytic Bacteremia is a not infrequent complication and often arises from the intestinal flora

The mucosa of the intestinal tract is relatively susceptible to radiation and is of course in constant contact with a wide variety of bacteria As a result ulceration of the intestinal tract occurs and the severity of the ulceration usually determines the character of the signs and symptoms which may range from slight diarrhea and vomiting to bloody diarrhea or rarely ileus with virtual necrosis of *much of the intestinal wall The mucosa of the* colon is somewhat more sensitive than that of the small intestine

Radiation injury to the skin is rarely seen in total body radiation because in those cases where a sufficient dose has been received to bring about characteristic cutaneous changes death usually occurs before they have opportunity to develop When present ulceration and edema are severe However some degree of erythema or transient epilation may occur Some of the Japanese exposed to the atomic bombs at Hiroshima and Nagasaki were epilated but in none who survived was the epilation permanent

Lymphoid tissue shows initial atrophy but may regenerate completely

The rate of healing of wounds or fractures is not significantly altered by radiation insufficient to impair the blood supply although radiation tends to inhibit phosphatase activity

Some fatal cases show atrophy of the adrenal cortex but significant changes in other endocrine glands aside from the hemorrhages incident to the hemorrhagic diathesis have not been observed The adrenal cortical atrophy may be partly related to the malnutrition resulting from the syndrome

Genetic Effects Transient sterility has been noted in the male but permanent sterility is not to be expected as an aftermath of total body radiation since the sterilizing dose for the testis is close to or above the lethal dose for man In women the sterilizing dose for the ovary is considerably more than the lethal dose so although transient sterility may occur permanent sterility would not be expected in survivors

Ionizing radiation is a very powerful mutagenic agent The effect of radiation in producing mutations is cumulative so it makes no difference from the genetic standpoint whether one receives 150 r at one time or spread out over a period of years For this reason special effort should be made to protect the gonads during therapeutic or diagnostic radiation The Committee on Genetics of the National Academy of Sciences has concluded that 10 r to the gonads of the mass of the population in addition to the background will still be commensurate with the good to be received from other aspects of this irradiation However x ray examinations particularly fluoroscopic examinations should not be carried out more frequently than is necessary Thus a fluoroscopic examination of the abdomen may involve a dose to the gonads of as much as 2 r The additional mutants produced by radiation are of the same general sort as those which occur spontaneously A dose either single or cumulative in the range of 30 to 80 r to the general population would probably double the number of mutations now experienced spontaneously It is assumed that *perhaps 2 per cent of total live births show some* minor or major genetic defect at the present time However our data on human genetics are as yet deplorably small

Treatment Treatment of this condition is in its infancy At present the most satisfactory therapy consists in liberal whole blood transfusions the use of antibiotics to control infection parenteral feeding including the amino acid complexes and the alleviation of such local abnormalities as may develop in the course of the general process Adrenal cortical preparations various vitamins and toluidine blue as an antiheparin agent have been suggested and may have slight value

Effects of Chronic Low level Radiation With the knowledge of radiation available today there is little accidental exposure to chronic low level radiation However it occurred in the past among radiologists and others occupationally exposed Radium poisoning has also appeared in some of those persons who drank or received parenterally water containing radium for its supposed therapeutic value The ingestion of radium in any form is now recognized as highly dangerous Chronic low level radiation may be expected to damage the bone marrow with resultant anemia or pancytopenia not infrequently preceded by a period of moderate leukocytosis and relative or absolute lymphocytosis There is in both man and animals a predisposition of the irradiated tissue to the development of malignant tumors In man leukemia osteogenic sarcoma fibrosarcoma and epidermoid carcinoma have been produced The incidence of leukemia is seven to ten times as high in radiologists as in physicians as a whole or the general population Chronic exposure of the skin particularly of the hands of radiologists has long been known to produce carcinoma Some persons who received irradiation of the thymus in infancy have developed carcinoma of the thyroid in early adult life

The radioactive isotopes used for therapy are so selected that they do not remain long in the body Hence they do not provide long continued radiation In the experimental animal malignant tumors

occur and objects within a radius of 100 ft may be struck Direct contact usually results in immediate death Persons nearby may be injured by the electrical current by burning from heated air or by the concussive force of compressed air

If patients die immediately autopsy findings are limited to burns and generalized petechial hemorrhage If patients survive for a period of days or longer post mortem examination reveals focal necroses of nerve spinal cord or brain involving both neurones and white matter with appropriate glial and vascular reactions

Manifestations Immediately after severe shock patients are usually comatose and apneic although the heart may continue to beat until anoxia leads to circulatory failure Surviving this stage patients are often disoriented and combative convulsions are frequent Blackened charred areas at the points of entrance and exit of the current may appear to be relatively small and well localized After a few days however huge sloughs often involving major blood vessels reveal the true extent of the destruction A frequent finding in victims of lightning is a characteristic lacy network of superficial arborescent burns or lightning prints on the skin These fade within 24 to 48 hr Late effects include various neurologic disabilities visual disturbances and of course the residual damage left by burns A curious finding in many victims of lightning is temporary flaccid paralysis of the lower extremities with loss of sensation so called keraunoparalysis which passes off in 12 to 24 hr This condition is often accompanied by blanching and coldness of the legs and is believed to be a result of severe vasoconstriction Hysterical symptoms are common after exposure to lightning Injuries to peripheral nerve spinal cord and brain often leave symptoms which may be confused with peripheral neuritis and multiple sclerosis The development of cataracts is another late complication

The wide use of electric shock in the treatment of psychiatric diseases (p 363) has led to occasional accidents These have been of two types Sudden death attributed to ventricular fibrillation has been observed in elderly patients with heart disease Fracture of vertebral bodies during the convulsive seizure has occurred this is preventable by the use of relaxant drugs

Laboratory Findings Leukocytosis with many large immature granulocytes in the peripheral blood is common after severe electrical shock Albuminuria is the rule hemoglobinuria has been reported in many cases probably secondary to severe burns Although elevation of cerebrospinal fluid pressure is often mentioned in electrical shock, it is an inconstant finding bloody spinal fluid occurs in some cases as a result of widespread vascular injury

Management Immediate *removal of the victim from contact* with the current is obviously important this should always be preceded by cutting off the source of the current when possible Rescuers should be insulated by rubber gloves or a thick layer of dry cloth or newspapers Many needless deaths have followed ill planned attempts to rescue the body of an individual already dead from electrical shock

Artificial respiration should be instituted immediately if the victim is not breathing The importance of this maneuver cannot be overemphasized In one series of 700 cases of electrical injury (Maclachlan) there were 479 with respiratory arrest of which 323 responded to artificial respiration The majority of patients who respond do so within 20 min but recovery after longer periods of time is frequent enough that manual or mechanical respiration should be continued for a minimum of 4 hr before giving up It has been estimated that a delay of 6 min in the institution of resuscitative measures increases the death rate in electrical shock by 80 per cent

Other treatment is supportive Stimulants should be used with caution during the first few hours because of the tendency of many patients to convulse There is no evidence that the frequently advocated procedure of cerebrospinal fluid drainage is beneficial Survivors of the acute episode often require extensive treatment for electrical burns secondary infection and massive hemorrhage as the devitalized tissues slough

Prevention An awareness of the danger of electricity is the most important factor in preventing accidents Proper insulation of appliances in the home and the use of rubber gloves and dry shoes when working with circuits will avoid disability and death Proper grounding of telephone and radio aerials against lightning should be routine In a thunderstorm the safest shelter is a house with windows and doors closed A closed automobile cave ditch or depression is relatively secure Hill tops riverbanks hedges and wire fences should be avoided Although a tree standing alone is dangerous the center of a wooded area is fairly safe

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show aplasia or the marrow may be hyperplastic with impaired maturation

The intestinal symptoms are caused by ulceration of the small as well as the large intestine Some ulceration is due to radiation necrosis of the relatively sensitive mucosal cells some to absence of granulocytes to control bacterial invaders from the intestinal contents

As far as can be judged from the Japanese survivors at the present time the great majority of those exposed who survive the acute stage will return approximately to normal Some cases of leukemia may be expected In those exposed to a significant flux of neutrons cataracts may develop

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108 ELECTRICAL INJURIES

Ivan L Bennett Jr

The first human fatality from accidental electrocution occurred in 1879 and was produced by an alternating current of 250 v Since that time continuing increase in household and commercial uses of electrical power has made accidents almost inevitable Injury and death from lightning have been occurring of course since time began

Etiology and Pathogenesis The end result of passage of an electrical current through the human body is unpredictable in the individual case Certain generalizations are possible however and many of the factors that influence severity of injury by electricity are known *Alternating currents* tend to produce tetanization of muscles and sweating (which lowers skin resistance) and *direct currents* produce electrolytic changes in the tissues It has been estimated that alternating is about four or five times as dangerous as direct current fatal electrocution can result from exposure to household circuits of 115 v at 60 cycles

The electrical conductivity of tissues parallels their water content consequently the vascular system and musculature are good conductors whereas bones peripheral nerves and skin offer high resistance The resistance of normal skin is lowered by *moisture* and this factor alone may convert what might ordinarily be a mild injury to fatal shock The *grounding* of the body at the time of contact is important It is well known that a person in water or on a wet surface is more susceptible to electrical injury The *pathway of the current* through the body is crucial Obviously an accident involving passage of current between a point of contact on the leg and the ground is likely to be less injurious than one in which the poles of the circuit are the head and a foot The *duration of contact* influences the outcome Because as mentioned an electrical current can stimulate skeletal muscle to contract a victim who has grasped an uninsulated wire may be unable to release it this is far more likely with alternating than direct currents and accounts in part for the greater danger of alternating circuits Sudden convulsive contraction of muscles can result in fractures of bone sometimes however it throws the individual clear of contact This can lead to additional mechanical trauma if the victim is thrown from a high place

In traversing the skin electrical energy of high tension currents is converted to heat When one considers that electric arcs with temperatures as high as 8000 C may be generated it is not surprising that fourth or fifth degree burns often result The term *electrical necrosis* is probably more appropriate than *burn* for this injury It has been suggested that the immediate damage is aggravated by vasospasm in adjacent tissues

The systemic effects of electricity are incompletely understood but in general low voltage produces ventricular fibrillation and death from circulatory failure and high voltage produces respiratory arrest High tension currents produce cardiac standstill but ventricular function resumes when the current stops and death is presumably attributable to injury of medullary centers Whether this neurologic damage is secondary to vasospasm or to increase in temperature of the brain or whether it is the result of direct injury to neurones is not known

A lightning flash is a rush of electrical energy (about 1 billion v and 20 000 amp) along a path more than a mile long and 18 to 20 ft in diameter The duration of the current is about 0 001 sec When the bolt reaches the earth secondary flashes

occur and objects within a radius of 100 ft may be struck Direct contact usually results in immediate death Persons nearby may be injured by the electrical current by burning from heated air or by the concussive force of compressed air

If patients die immediately autopsy findings are limited to burns and generalized petechial hemorrhage If patients survive for a period of days or longer post mortem examination reveals focal necroses of nerve spinal cord or brain involving both neurones and white matter with appropriate glial and vascular reactions

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PART SIX

Diseases Due to Biologic Agents

Section 1 Basic Considerations

109 AN APPROACH TO INFECTIOUS DISEASES

Ivan L Bennett Jr

The vast majority of human and animal diseases of known etiology are produced by biologic agents viruses rickettsiae bacteria fungi protozoa or nematodes No small part of the past and present importance of infectious diseases in medical practice is attributable to their enormous frequency and the public health implications of the contagiousness of many of them It is also of note however that development in sanitary engineering vector control techniques of immunization and specific chemotherapy have modified the situation favorably While important exceptions remain infectious diseases as a class are more easily prevented and more easily cured than any other major group of disorders

THE PARASITE AND THE HOST

The complex interaction between microorganism and man that results in infection and disease has been subjected to extensive study Much has been learned about the initiation of the process the ways in which microbes produce tissue injury the influence of specific immunity and "nonspecific" resistance of the host and mechanisms of recovery Unfortunately it is not yet possible to transfer in any specific way much of the information thus far acquired to the individual human patient with an infectious disease In a textbook of medicine therefore it seems appropriate to emphasize those general aspects of the host parasite relationship that form a basis for diagnostic procedures that are of importance in deriving therapeutic principles or that help explain the epidemiology of infection and infectious disease This necessitates omitting from these pages discussion of many highly significant and interesting experimental studies controversial issues and theoretic or incompletely established concepts The bibliography at the end of the chapter contains excellent reviews of these important subjects

Infection and Clinical Disease It is well known that microorganisms of different species or different strains of the same species vary widely in their capacity to produce disease and that human beings are not equally susceptible to the disease caused by a given bacterium or virus Furthermore while a specific infectious disease will not occur in the absence of the causative organism the mere presence of the organism in the human body does not lead invariably to clinical illness Indeed it is now obvious that the production of symptoms in man by many parasites is an exceptional event rather than the rule a "subclinical infection" or "carrier state" being the usual host parasite relationship *Disease* in a clinical sense is not synonymous with the presence of the organism or *infection* in a microbiologic sense

Mechanisms of Injury It is customary to refer to bacteria or other microorganisms that are capable of producing disease as *pathogenic* *Virulence* the ability to produce harmful effects in the host is distinguished carefully from *invasiveness* the ability to spread and disseminate in the body For example *Clostridium tetani* is pathogenic and by virtue of its exotoxin highly virulent but it is almost completely lacking in invasiveness These distinctions are valuable in microbiology and experimental pathology but they often mean relatively little at a clinical level in an individual patient Under certain circumstances and in certain anatomic locations mildly "pathogenic" organisms can produce fatal disease or highly "pathogenic" species can dwell and multiply without producing any harmful effect

A few parasites produce *toxins* that account for the tissue damage and physiologic alterations of infection *Hypersensitivity* to components of the parasite is demonstrable in several infections but in relatively few has sensitization been shown to account for the manifestations of disease For a large proportion of pathogenic agents an explanation of their damaging effects upon the host is incomplete or wholly lacking Generally therefore the aim of therapy is to stop multiplication or to kill the parasites with appropriate drugs in diseases caused by toxin producing organisms the use of antiserum (as in tetanus or diphtheria) is the definitive procedure chemotherapy being secondary

The *tropism* of certain pathogenic organisms their tendency to *localize in certain cells or organs* and to produce damage is unexplained in most instances Clinically however the presence of disease in a specific anatomic site or a combination of symptoms referable to certain organs often suggests the identity of the causative organism Similarly in the presence of disease known to be caused by a given agent complicating involvement of other tissues can be anticipated or predicted

Frequently the proper management of infectious disease involves the use of techniques completely unrelated to microbiology or chemotherapy in an effort to support the function of damaged organs Survival in poliomyelitis may depend upon treatment of respiratory failure the management of heart failure in endocarditis is sometimes a greater problem than the eradication of the causative organism and in epidemic hemorrhagic fever or Weil's disease maintenance of fluid and electrolyte balance during the stage of acute renal failure is the important therapeutic objective

Resistance and Susceptibility Many so called "host factors" are known to influence the likelihood that disease will occur if organisms enter the tissues or if infection becomes established to play a determining role in the final outcome—recovery or death

In experimental animals *sex strain age route of infection* the presence of *specific antibody other diseases nutritional state* and the use of such procedures as exposure to ionizing radiation or high environmental temperature or administration of mucin nitrogen mustard adrenal steroids epinephrine xerosin and metabolic analogues can be shown to exert a profound effect upon infection by bacteria viruses and other agents

In man these factors are no less impressive although controlled studies are lacking for many Alcoholism diabetes agammaglobulinemia the nephrotic syndrome malnutrition chronic administration of adrenal hormones chronic lymphedema ischemia the presence of foreign bodies such as bullets calculi or bone fragments obstruction of a bronchus the urethra or any hollow tube agranulocytosis various blood dyscrasias and many other circumstances influence susceptibility to systemic or local infection Furthermore in those instances where the extenuating condition is remediable the probability of recovery is enhanced

Racial differences in susceptibility such as the poor resistance of the Negro to tuberculosis or the peculiar resistance of Negroes to malaria caused by *Plasmodium vivax* are well established in several infections The increased frequency and severity of some infections in children others in pregnant females still other in the aged are familiar clinical facts

Prior contact with an organism whether by active infection or by artificial immunization increases resistance to some infections such as measles and poliomyelitis but seems to have little influence on resistance to others such as gonorrhea and acute coryza

In the chapters that follow the variations in human resistance to specific infectious agents are discussed in detail

Finally it must be emphasized that present knowledge of the factors involved in human resistance and susceptibility extends little beyond an *empirical tabulation of clinically observed relationships* The attractive explanations that have been suggested including changes in physical or chemical activity of phagocytes antibacterial substances such as lysozyme properdin and phagocytin *qualitative or quantitative alterations in serum* proteins disordered metabolism at the cellular level products of tissue injury that influence vascular permeability and several others remain for the most part in the realm of hypothesis

The profound influence of "host factors" upon the infectious process makes it clear however that if our understanding of them ever reaches a point that enables us to control them in a predictable fashion we will enter a new era in the management and control of infectious disease There is no more important and fertile field for investigation in medicine

PATHOGENESIS OF INFECTION

With relatively minor variations the development of an infectious disease follows a consistent pattern The parasites enter the body through the skin nasopharynx lung intestine urethra or other portal and a regular sequence ensues Once established in the host the organisms can multiply and in so doing establish a *local* or *primary lesion* From this site there may be *local spread* along fascial planes or tubular structures such as a bronchus or ureter The next step is *systemic spread* of the microorganisms by the circulating blood which they reach by direct invasion of vessels (a relatively unusual occurrence) or by the common method of being borne in lymph to the thoracic duct and entering the venous system In the blood stream they spread to other tissues and can produce *distant* or *secondary lesions* In infections such as tetanus and diphtheria distant lesions are produced by toxins elaborated at the primary lesion without systemic spread of the parasites The infectious process may terminate in recovery or death at any stage the local lesion systemic spread or distant lesion

The apparent inconsistency of this pattern in clinical medicine is attributable to the fact that *the infection has been recognized as a clinical entity* only at the stage when symptoms are most likely to appear For example pneumococcal pneumonia is a local lesion and the distant lesion pneumococcal meningitis is referred to clinically as a *complication* In meningococcal infections the local lesion a nasopharyngitis is rarely symptomatic and has no status as a clinical entity but the stage of spread meningococcemia and the commonest distant lesion meningitis are clinical enti

ties A rarer distant lesion arthritis is called a complication In subacute bacterial endocarditis both the local lesion in the gums and the stage of spread are insignificant the distant lesion is the clinical disease In a patient who has osteomyelitis a clinical entity a recent furuncle may be referred to as a *predisposing factor* In another patient with extensive furunculosis who develops osteomyelitis the infection in bone may be regarded by the clinician as a complication of the superficial infection The stages mentioned are in no way limited to bacterial diseases the primary lesion of poliomyelitis is intestinal viremia may occur without neurologic involvement or a distant lesion the classic infantile paralysis may be established

Because of established clinical usage and terminology based upon the symptomatic illness that leads patients to seek medical aid the consistency of this general sequence in the pathogenesis of infection is often not recognized However the concept is useful to the clinician and offers some basis for systematizing what may otherwise seem to be a miscellaneous collection of unrelated clinical signs and symptoms

CLINICAL MANIFESTATIONS OF INFECTIONS

So varied are the disorders attributable to infection or infestation of man by lower organisms that generalization about them is difficult The clinical manifestations of infection can duplicate those of diseases of any other etiology On p 72 there is a discussion of certain clinical features highly suggestive of infection including abrupt onset fever chills myalgia photophobia pharyngitis acute lymphadenopathy or splenomegaly gastroenteritis and leukocytosis or leukopenia It is obvious that the presence of one several or all of these features does not constitute proof of the microbial origin of illness in a given patient Conversely serious even fatal infectious disease can exist in the absence of fever or the other signs and symptoms mentioned

While there is no infallible clinical criterion of infection it is still possible to recognize accurately many specific infectious diseases from information obtained by *history physical examination blood count* and *urinalysis* The importance of interrogation about past illness predisposing factors such as alcoholism familial disease exposure to ill persons contact with animals or insects ingestion of contaminated food type and order of onset of symptoms and recent or remote residence in endemic areas is discussed in subsequent chapters for specific diseases and etiologic agents Cardinal physical signs are also described for each entity

It is fitting to acknowledge our ignorance of the mechanisms that produce most of the signs and symptoms of human infection As discussed on p 69 the pathogenesis of fever is poorly understood The physiologic alterations underlying "malaise postinfectious asthenia toxicity" and other common complaints are completely mysterious We have little or no idea about the factors responsible for the leukocytoses or leukopenias that characterize certain infections Why the rash of typhus begins on the trunk while that of another rickettsiosis Rocky Mountain spotted fever begins on the extremities is unanswered It cannot be said that failure to understand the production of these manifestations impairs their clinical usefulness in differential diagnosis but it is probable that understanding would bring with it clues to more accurate diagnosis and better management

DIAGNOSTIC PROCEDURES

When dealing with diseases produced by living agents it is soon evident that confirmation of a presumptive diagnosis or sometimes the first suggestion as to the etiology of illness often depends upon laboratory procedures The availability of a multitude of laboratory tests in the modern hospital has not made it possible to substitute a "routine lab work up for history physical examination and observation of a patient s course Indeed the information derived from these procedures is the only reasonable basis for selecting the tests to be performed by the laboratory

The importance of roentgenographic changes alterations in chemical constituents of the blood and tests of the functional capacity of organs such as the liver and kidney is as great in infectious disease as in illnesses of other etiologies and needs no discussion here The specific procedures for the diagnosis of infectious disease involve *direct demonstration of the causative organism* or *proof of its presence by indirect means*

Demonstration of the Organism In bacterial diseases it is often possible to find the causative organism by *microscopic examination of properly stained preparations of sputum spinal fluid and other body fluids* This simple procedure is often neglected as an unnecessary bother when material is being sent for bacteriologic culture but *it is a* most valuable source of immediate information In many diseases the etiologic agent cannot be cultured (bartonellosis) and in others *isolation is* time consuming (tuberculosis blastomycosis) The diagnosis of meningococcal infection (p 870) by finding the organism in fluid *from skin lesions or in* the buffy coat or the finding of *Hemophilus influenzae* in stained smears of cerebrospinal fluid enables the clinician *to initiate* specific chemotherapy immediately with assurance that the regimen is the proper one

Direct examination of bone marrow is a useful method for demonstrating organisms in some diseases kala azar histoplasmosis and tuberculosis being examples In protozoan (amebiasis malaria) and parasitic diseases (schistosomiasis filariasis) *direct examination of blood feces or urine* is the only specific method for establishing a diagnosis

There are also infections in which the *detection of characteristic cytologic changes or the causative organism itself in smears or histologic sections of biopsy material* can be the quickest method for diagnosis *Tubercles and tubercle bacilli in lymph* nodes or liver biopsy material leprosy bacilli in skin or nasal scrapings inclusion bodies in the skin lesions of varicella or variola and exudate of inclusion blenorrhea "Warthin" cells from the nasal mucosa in measles schistosome ova in punch biopsies of rectal mucosa and the Councilman bodies of yellow fever in liver are examples In addition characteristic histologic changes make it feasible to identify the lesions of chancroid syphilis lymphogranuloma venereum cat scratch disease or viral hepatitis in biopsy specimens Indeed even in diseases where other reliable tests are available diagnosis by histologic examination is sometimes the most rapid method an example being the characteristic muscle lesion of Weil s disease (p 1015)

Special Microscopic Techniques *Dark field examination* of material from genital lesions for the spirochete of syphilis is a well known procedure In several other spirochetal diseases including leptospirosis the dark field technique can be useful but experience in recognition of the organisms is necessary for correct interpretation of findings

Fluorescence microscopy in which the causative organisms can be recognized and identified rapidly by the use of fluorescent antibody preparations (the *Coons technique) has not been applied to general clinical work With further refinement and simplification* it may eventually prove to be extremely useful in diagnosis

Culture and Animal Inoculation Specimens for bacteriologic culture should be collected *before the initiation of chemotherapy* The material to be cultured—sputum pus blood or bone marrow—should be selected on the basis of the suspected infections and the precise cultural techniques employed—media CO incubation anaerobic incubation etc —must be decided upon in a similar fashion

In several infections including Weil s disease rat bite fever certain mycoses tuberculosis and the rickettsioses isolation of the etiologic organism can be made by *inoculation of appropriate material into mice or guinea pigs* This is a cumbersome procedure for routine use but in selected instances it should be employed As mentioned in subsequent chapters many viruses can be isolated by inoculation of appropriate animals This is rarely feasible for ordinary clinical diagnosis and for several agents is hazardous

Facilities for *isolating viruses by inoculation of tissue cultures* are available in a few centers but this method is likely to remain an investigative tool until it can be simplified and adapted to general use at a clinical level

Blood Cultures and Bacteremia Because of the peculiar clinical importance of demonstrating bacteria in the blood stream and because there are varying opinions about optimal timing and sites of sampling for blood cultures it is of practical importance to the clinician to understand something about the mechanisms of bacteremia

Excepting intravascular infections (bacterial endocarditis or endarteritis mycotic aneurysm suppurative thrombophlebitis) the entry of bacteria into the circulation occurs almost invariably through the lymphatic system Consequently when bacteria multiply at a site of local infection in the tissues the likelihood of bacteremia parallels the occurrence of local conditions that favor drainage of lymph from the area to the thoracic duct and eventually the venous blood These factors include the number and anatomic arrangement of local lymph vessels accumulation of fluid and increase in tissue pressure (a prominent feature of the inflammatory response) and exercise or massage of the part

Once bacteria enter the blood they are removed rapidly by the fixed phagocytes of the reticulo-endothelial system in the liver and spleen and by engulfment in polymorphonuclear leukocytes in capillaries especially those of the lung

Clinically bacteremia can be transient intermittent or continuous Many transient bacteremias result from manipulation of infected or contaminated tissues common *examples being instrumentation of the genitourinary tract tonsillectomy dental pro*cedures and massage or surgical incision of furuncles or abscesses In the vast majority of instances the sudden discharge of bacteria into the blood produces no symptoms or at most a rigor and brief fever and the organisms are promptly dealt with by the removal mechanisms already mentioned The great importance of these man made bacteremias is their role in producing bacterial endocarditis (p 970) in patients with endocardial damage

Transient bacteremia accompanies the early phase of many *infections In pneumococcal pneu*monia the typical rigor at onset is a result of transient bacteremia In most cases with localization of the pulmonary lesion blood cultures rapidly revert to negative The poor prognosis assigned to patients with pneumonia who continue to have positive blood cultures is not based upon any danger from the mere presence of organisms in the blood as much as it is upon bacteremia as a re

flection of spreading infection in the lung itself

A sudden single influx of microorganisms into the blood stream may be followed by a shaking chill and fever However there is a "lag period" of 30 to 90 min before the febrile response (similar to the lag in pyrogen fever p 70) During this delay the bacteria are usually promptly removed from the circulation by phagocytosis and consequently a blood culture taken at the time of the rigor may be negative Failure to recognize this sequence led for many years to the idea that chilling after instrumentation of the urethra was the result of some peculiar property of the bladder and even today the term catheter fever" is sometimes employed *Failure to obtain growth in a blood culture taken during a chill does not rule out bacteremia as a cause of the fever* Another frequent effect of transient bacteremia is the production of transient severe leukopenia followed by a polymorphonuclear leukocytosis for a few hours *Peripheral leukocyte counts made during the few hours after a chill may give information that is erroneously interpreted in diagnosis*

Continuous bacteremia is a feature of the first several days of typhoid fever of brucellosis and of intravascular infections such as endocarditis

Blood cultures should be taken at frequent intervals in patients with febrile disease of unknown etiology in general an attempt should be made to obtain blood *before* an expected rise in fever or chill When a patient is suspected of bacterial endocarditis or another of the diseases in which bacteremia is constant two to four cultures daily for 2 to 3 days are more than sufficient to establish diagnosis and treatment in such cases should not be withheld for a longer period

There is no evidence that arterial blood possesses any advantage over blood from the antecubital veins for culture Suspected bacteremia is sometimes mentioned as a contraindication to diagnostic lumbar puncture because of the possible development of meningitis but clinical evidence does not support this idea Culture of bone marrow is occasionally superior to peripheral blood for recovery of organisms in typhoid brucellosis and rare cases of subacute bacterial endocarditis While it is common practice to make pour plates of blood and to quantitate bacteremia in terms of a certain number of colonies per milliliter of blood the results of this rather cumbersome procedure have no diagnostic or prognostic significance and it has no advantage for routine use In typhoid for example the number of bacilli in the blood rarely exceeds 25 to 30 per milliliter and bears no relationship to the severity of illness When blood cultures are taken for diagnostic purposes some should be incubated in carbon dioxide and a sample of blood should also be cultured in thioglycollate broth or some other anaerobic medium Anaerobic cultures are especially important in women with puerperal or postabortal infections

Immunologic Methods These diagnostic methods are intended to supply evidence of past or present infection by demonstrating antibodies in serum or other body fluids by showing changed reactivity of the host (hypersensitivity allergy) to products of the organism or rarely to detect components of the causative organism in the body The reader is referred to standard texts of immunology for detailed discussion of the nature of antigens and antibodies the cellular origin of antibody and the complex interactions of antigen antibody systems Emphasis here is directed toward the interpretation of immunologic tests commonly used for clinical diagnosis

Serologic Tests The finding on a single occasion that a patient s serum contains antibody that reacts with a certain antigen merely indicates that the patient has had previous contact with the antigen or a closely related substance For this reason with rare exceptions the clinical interpretation of serologic tests depends upon serial determinations If the antibody titer is found *to rise or fall significantly* one can then be reasonably sure that the response is a result of recent or current contact with the antigen In subsequent chapters the need for serologic testing of acute phase and convalescent serum is emphasized repeatedly *In any patient with a puzzling illness a sterile specimen of serum should be preserved in a frozen state so that it can if necessary be studied and compared with serum collected at a later date*

Prior contact with an antigen can be the result of past artificial immunization with vaccines interpretation of serum agglutinin titers for typhoid bacilli i often made difficult or impossible by prior immunization The occurrence of the so-called anamnestic reaction" a supposed nonspecific stimulation of antibody formation by an acute illness (e g a rise in brucella agglutinins in a patient with acute tularemia) is now known to result only when the two organisms are antigenically related and rarely presents a serious problem The vibrio of cholera contains an antigen similar to that of brucella and surprisingly high levels of brucella agglutinins have been seen in servicemen immunized with cholera vaccine

The exact methods employed for detecting antibody rises in various infections have been selected empirically on the basis of the ease of performing the test as well as on careful study to correlate the results of the test with other diagnostic criteria in patients Therefore the fact that one agent is detected by a precipitin technique another by agglutination of whole organisms or the production of capsular swelling and still another by complement

fixation is a practical matter of convenience and bears no necessary relationship to the agent the type of infection produced or basic pathogenesis By coating some particulate material such as erythrocytes or collodion particles with antigen derived from a certain organism antibody can sometimes be demonstrated by an agglutination test rather than by some more complex method

Particular properties of the causative organism can sometimes be utilized to devise a simplified clinical test for antibody Two striking instances of this are widely used The ability of influenza and related viruses to clump erythrocytes (see p 1050) makes possible the demonstration of antibody to virus by merely testing the capacity of a patient's serum to prevent the agglutination of red cells by suspensions of virus the so called "hemagglutination inhibition reaction Similarly because many microorganisms possess hemolytic components or toxins the assay of a patient's serum for capacity to prevent lysis of red cells is a convenient and simple clinical test for antibody The antistreptolysin O test in group A beta hemolytic streptococcal infections (p 846) is an example of this

In a few infections predominantly those caused by viruses the only reliable serologic test is a *neutralization* or *protection* test an assay of the protection afforded by the patient's serum against active infection in experimental animals or in tissue culture This technique is time consuming and is *usually performed only in special diagnostic centers*

Some mention of nonspecific serologic changes may serve to emphasize again that clinical laboratory tests have come into use *only because they have been found to correlate reasonably well with clinical findings* In several diseases it has been found often accidentally that there develops serum antibody that will react with antigens derived from sources other than the etiologic agent (which may actually be unknown) Common examples are het*erophil agglutinins in infectious mononucleosis (p* 1151) cold agglutinins in some forms of nonbacterial pneumonia (p 1046) and the agglutination of certain strains of *Proteus* bacilli by serum of patients with rickettsial diseases (p 1051) The outstanding example of a clinically useful nonspecific serologic test is the Wassermann reaction for syphilis This test and its modifications are performed with antigens derived from source completely unrelated to the spirochete that causes the disease Because of their simplicity they are still used in preference to more complicated and admittedly more accurate techniques that utilize the *Treponema pallidum* itself (p 1000)

In summary the results of serologic tests must be interpreted in the light of other information about the patient including such factors as previous immunizations and illnesses the possibility of exposure to chemically but etiologically unrelated antigens and the importance of a changing titer *in serial tests as opposed to a single isolated observation*

Skin Tests Exposure to antigens of certain types by various routes and under circumstances not completely understood often results in the development of *immediate (anaphylactic atopic) hypersensitivity or delayed (bacterial tuberculin) hypersensitivity* (see p 1159 for further details)

Active infection with some but not all bacteria and viruses results in delayed hypersensitivity to the infecting agent in some but not all individuals Clinically the detection of this allergic state is accomplished by intradermal injection of the organisms or some component of them in a sensitive person there will appear induration and erythema at the local site within 24 to 48 hr If an individual is highly sensitive *or if the amount of antigen injected* is excessive there may be extensive local inflammation with necrosis vesicle formation edema regional lymphadenopathy and even systemic manifestations of malaise and fever Antigens prepared in concentrations unlikely to provoke severe reactions are generally available for intradermal testing for tuberculosis leprosy mumps lymphogranuloma venereum cat scratch disease chancroid brucellosis tularemia glanders toxoplasmosis blastomycosis histoplasmosis coccidioidomycosis *and many other infections The immune* reaction to vaccination (p 1061) is also an example of delayed dermal hypersensitivity

The reliability specificity and usefulness of the individual tests differ and are discussed in the chapters on specific infections However certain general principles apply to their use and interpretation

1 They are highly useful in epidemiologic surveys as indicators of the incidence of infection in a population

2 In most individuals dermal reactivity persists *for many years or for life A single positive test* means only that at some past time the individual was exposed to the organism (or a closely related one) Unless supplementary information in the form of clinical findings cultural studies or more specific serologic data bear out the presence of active infection a diagnosis of the disease is not justified

3 The appearance of a positive dermal reaction in an individual known to have been nonreactive a short time before is good evidence of recent infection this is becoming a useful method for detecting early tuberculosis

4 A *negative intradermal test does not rule out past or present infection* For unknown reasons patients with measles Hodgkin's disease or sarcoidosis often develop a state of anergy or inability to react to intradermally injected antigens

In several diseases dermal sensitivity develops after weeks or months of infection an important example of this is acute histoplasmosis (p 991) in which patients can be acutely ill for many weeks without showing a positive skin test The skin test to coccidioidin is always negative in disseminated coccidioidomycosis (p 988) and in far advanced or miliary tuberculosis in elderly patients failure to react to intradermal tuberculin in the usual amounts employed for testing occurs in as many as 10 to 15 per cent of the cases

Intradermal injection of antigens derived from sources other than microorganisms usually produces an immediate "wheal and erythema" reaction which subsides promptly The greatest clinical usefulness of this type of reaction is in the detection of allergy to foreign serums pollens and animal dander (see p 1160) The skin tests developed for demonstrating infestation with helminths (trichinosis filariasis) produce reactions of the immediate type in allergic individuals but the antigens employed are so nonspecific that they are of little use in diagnosis

THE IMPORTANCE OF SPECIFIC DIAGNOSIS IN INFECTIOUS DISEASES

Medicine and Microbiology The diagnostic procedures employed for infectious diseases are no more absolute than those in other diseases they cannot be blindly equated with the science of microbiology The responsibility for interpreting the facts supplied by the bacteriologist immunologist and virologist in the total context of a patient s illness remains that of the physician A positive tuberculin skin test certainly does not indicate that a patient has active tuberculosis The finding of *Candida albicans* (monilia) in a stool culture does not necessarily mean that a patient s diarrhea is caused by intestinal moniliasis The presence of staphylococci in nasal cultures from a patient with headaches does not establish a diagnosis of staphylococcal sinusitis A throat culture containing beta hemolytic streptococci does not rule out diphtheria nor does such a culture establish that a febrile illness in a patient with mitral stenosis is a recurrence of acute rheumatic fever and not bacterial endocarditis A positive serologic test for syphilis may be the first sign of incipient lupus erythematosus The decisions in such matters must be made by the patient s physician

Chemotherapy The next chapter discusses the antimicrobial drugs in detail The impact of chemotherapy upon mortality and morbidity from infection and upon epidemic disease is now a matter of historical record These therapeutic agents however have in no way lessened the importance of specific diagnosis indeed their availability has increased the need for obtaining exact etiologic information It requires but a moment s reflection to realize that the substitution of a prescription for a broad spectrum antibiotic or a quick injection of penicillin for the systematic collection of facts and thoughtful consideration of diagnostic possibilities is fallacious unwise and dangerous Numerous antibiotics with overlapping spectrums are now available dosages for different infections vary widely certain diseases are best treated with combinations of drugs and the drugs themselves are potentially dangerous They should never be prescribed as placebos antipyretics or substitutes for diagnosis In the vast majority of instances where this is done patients recover just as they would if no therapy had been given and the drugs are wasted More important inadequate dosage or the wrong agent given blindly may suppress symptoms temporarily without curing make isolation of the etiologic agent difficult and delay the recognition of the true nature of an illness and the institution of curative treatment Finally to expose a patient to the risk of drug reaction without proper indication is inexcusable on the part of the physician whether the drug is an antibiotic a sedative a laxative or a narcotic

Epidemiologic and Other Considerations Just as the decision to administer antibiotics to a patient with a febrile illness of presumed infectious etiology must be made on an individual basis the selection of cases in which extensive cultural and serologic testing is required is a matter of judgment The majority of common "grippelike" illnesses subside spontaneously and symptomatic treatment is sufficient However because of this tendency toward spontaneous recovery and also because the results of serologic tests even if diagnostic may not be available until a patient is convalescent there are many who regard continued effort to determine the specific etiology of illness as an impractical "academic" procedure Such an attitude fails to recognize that the responsibility of the physician extends beyond the individual patient to include the community Furthermore the physician has a responsibility to himself For example a patient recently recovered from "viral pneumonitis" may feel that his physician has cared for him competently and well The doctor himself may feel that he has discharged his professional duties properly and that his having refrained from giving the patient antibiotics for what was clinically a virus disease and therefore unlikely to benefit from chemotherapy was a laudable act of forebearance However if a serologic test is reported a few days later as showing that the patient s serum has shown a rise in complement fixing antibody against psittacosis virus the situation might change The patient himself would continue to be well but a search for

the source of the disease such as the patient's pet parakeet would certainly be indicated and future illnesses in others might be prevented Furthermore the physician would benefit from being reminded that antibiotics are effective in a few of the viral diseases and that pneumonitis is one of the clinical situations in which this possibility should be considered

Other examples of the practicality of academic procedures could be cited There are extremes in everything and in the final analysis the decision about the individual case must be made by the attending physician using his best judgment based on some of the factors that have been mentioned

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110 CHEMOTHERAPY OF INFECTION

Louis Weinstein

The *chemotherapy of infection* as discussed in this chapter may be best defined as the use of drugs to suppress the growth of or kill pathogenic microorganisms in the animal body The chemotherapeutic agents at present available for the treatment of infectious diseases can be divided into two main groups on the basis of their origin (1) those which are totally synthetic substances—sulfonamides sulfones quinacrine arsenic compounds and isonicotinic acid hydrazide for example (2) those which are elaborated by various types of microorganisms (some have been synthesized subsequent to their initial isolation)—penicillin streptomycin chlortetracycline (Aureomycin) and chloramphenicol (Chloromycetin) for example The latter agents are classified as antibiotics

THE CHEMOTHERAPEUTIC AGENTS

To be of practical value in the treatment of infection a drug must exert its effect upon the invading microorganism without seriously damaging the cells of the host It is remarkable that so many agents with this selective activity have been developed As far as is known all chemotherapeutic agents exert their effects in the intact animal by acting directly upon the parasite and not by enhancing the natural defense mechanisms of the host The principal action is a retarding of the rate of growth of bacteria (bacteriostasis) which enables the normal defense mechanism of phagocytosis with or without the aid of an antibody to deal with them When present in sufficient concentration some drugs may also kill bacteria in vivo as well as in vitro When certain chemotherapeutic substances are given in large doses early in an infection depression or total elimination of the immune response to the invading microorganism may follow

Quinine emetine heavy metals organic iodides and other synthetic agents are used extensively in the treatment of protozoal and helminthic infections information concerning these agents is presented in the chapters dealing with these specific diseases The discussion to follow will be limited to two classes of chemotherapeutic substances the *sulfonamides* and *sulfones* (effective for the most part only against bacteria) and the *antibiotics* (active against bacteria rickettsiae amebas and some of the larger viruses) Brief mention will be made of two tuberculostatic drugs which are neither sulfonamide compounds nor antibiotics para aminosalicylic acid and isonicotinic acid hydrazide

THE SULFONAMIDES AND SULFONES

The sulfonamide compounds have been used in clinical medicine since 1937 and a number of agents of this type have been developed A few

have been found to be effective in some diseases and relatively nontoxic in man Some of the more important and useful sulfonamides include sulfapyridine sulfathiazole sulfamethazine sulfadiazine sulfamerazine and Gantrisin among those which are rapidly absorbed from the intestinal tract and sulfaguanidine Sulfasuxidine and Sulfathalidine which are poorly removed from the bowel At the present time the most widely used products are sulfadiazine and sulfamerazine and the nonabsorbable Sulfasuxidine and Sulfathalidine

The sulfonamides although less useful at present because of the availability of much more effective antibacterial agents are very valuable in the management of certain infections They are the drugs of choice in meningococcal meningitis and bacillary dysentery They are often applied with varying success in instances of urinary tract infections which have not responded to the use of various antibiotics Sulfonamides are employed in the prophylaxis of recurrent rheumatic fever and urinary tract infection following catheterization These agents are used at times in conjunction with other antibacterial substances in the treatment of severe systemic infections Although there is a strong clinical impression that an additive chemotherapeutic effect may be produced by such a combination data from carefully controlled studies are meager

The sulfonamide compounds at present employed for the treatment of systemic infections are readily absorbed from the gastrointestinal tract and are probably best administered by this route to the conscious patient Preparations for either intramuscular or intravenous use are also available and consist of the sodium salts of the drugs They are much more soluble than the primary compounds and are given most frequently when the drug can not be administered orally In the treatment of meningococcal meningitis intravenous or subcutaneous injection of the first one or two doses of sulfadiazine appears to produce more rapid defervescence than when treatment is initiated by the oral route Liquid preparations made palatable by the addition of flavoring materials are useful in treating young children For most of the infectious diseases in which the sulfonamides are of value the duration of therapy should be no less than 1 week

An adequate concentration of the sulfonamides must be maintained in the blood and tissues to produce effective bacteriostasis A blood level of 10 to 12 mg per 100 ml is sufficient for the management of most of the susceptible infections The interval between separate doses is usually short 4 to 6 hr If the drugs are given by the parenteral route the size of each dose is reduced and the interval between doses increased in order to avoid the development of excessively high plasma levels It is important that the concentration of drug in the blood be estimated at frequent intervals in order that the quantity administered may be adjusted properly this is relatively simple and accurately determined by colorimetric methods

Most of the sulfonamide compounds are widely distributed in the body Exceptions are Sulfasuxidine and Sulfathalidine which are poorly absorbed and largely excreted in the feces After absorption the major metabolic alteration is acetylation of the primary amino group Sulfonamides are excreted by the kidney chiefly by glomerular filtration The distribution of these compounds in the body depends upon the extent to which each becomes fixed to plasma and tissue proteins Derivatives which are not firmly bound tend to be distributed evenly in total body water and thus reach high concentrations in tissue cells whereas those with a tendency to binding are concentrated in the plasma

The bacteriostatic activity of the sulfonamides is presumed to be related to their antimetabolic properties Para aminobenzoic acid (PABA) which inhibits the antibacterial effect of most of these agents is an essential metabolite of microorganisms PABA is part of the molecule of folic (pteroylglutamic) acid It has been suggested that the sulfonamides prevent the incorporation of PABA into the pteroylglutamic acid molecule These drugs probably have other important actions in interfering with the normal metabolism of bacteria They probably do not always act on a single stage in the chain of enzymatic reactions involved in cell metabolism but may inhibit several steps

The principal toxic effects of the sulfonamides are hypersensitivity reactions and injury to the kidneys Hypersensitivity may be manifested by fever rash granulopenia or depression of other components of the bone marrow These reactions may develop any time after the first week of therapy or even earlier in patients who have received the drug previously Sensitivity to one type of compound frequently confers sensitivity to others Damage to the kidney may result from two types of injury (1) precipitation of the sulfonamide especially its acetylated form in the tubules (2) development of a reaction of hypersensitivity in the kidney with the production of lower nephron nephrosis Crystallization of the drug in the renal tubules is most likely to occur when an inadequate quantity of fluid has been ingested or when the reaction of the urine is acid since the solubility of both acetylated and free forms is considerably greater in a neutral or alkaline medium One obvious method of avoiding renal injury is to maintain a copious urine output—at least 1,200 ml per day Another procedure is to produce an alkaline urine by the

oral administration of 12 to 15 Gm sodium bicarbonate per day. With the increase in solubility of the sulfonamide in the urine the excretion of the drug is simultaneously more rapid. The concentration is thus lowered in the blood and this makes necessary the administration of larger quantities in order to raise the blood level to the point of maximal effectiveness. In many clinics, therefore, alkalinization of the urine is not carried out. Another method of preventing precipitation in the urinary tract is to administer two or three sulfonamides concomitantly, since the solubility of each is independent of the presence of the others. This, however, may have a disadvantage since in vitro at least combinations of sulfonamides often exhibit much less antibacterial activity than the drugs used singly. Lower nephron nephrosis, a rare complication of sulfonamide therapy, usually occurs in patients who have taken one of these drugs in the past; it may follow the ingestion of as little as 1 Gm of the agent. It is a totally unpredictable and unavoidable accident for which there is no specific therapy. Another rare but serious manifestation of sulfonamide toxicity is acute hemolytic anemia. This may develop within 48 hr of therapy and is manifested by a rapid fall in the number of erythrocytes, rising icterus, high fever and hemoglobinuria. Drug administration should be discontinued at once and blood transfusions given.

Sulfadiazine (2-sulfanilamidopyrimidine) is absorbed from the gastrointestinal tract slowly and incompletely. Excretion of this agent by the kidney occurs more slowly than with some of the other sulfonamides. It may be recovered in pleural, synovial, pericardial, peritoneal and edema fluids, the tissue concentration being 60 to 75 per cent of that in the plasma. About 50 per cent of the drug is bound to protein but there is no correlation between this and the clinical effectiveness. Only small amounts of the agent are acetylated. Sulfadiazine appears in the urine in both the free and acetylated forms. Neither is very soluble and crystalluria is common. For most types of systemic infection in adults sulfadiazine is administered in a dose of 4 to 6 Gm per day following an initial dose of 4 Gm. In young children 0.065 to 0.1 Gm per lb of body weight per 24 hr usually produces an adequate effect; the initial dose should be about one half of this quantity.

Sulfamerazine (4-methyl-2-sulfanilamidopyrimidine) is absorbed more rapidly and completely from the gastrointestinal tract than sulfadiazine. For these reasons the "loading" dose need be only 2 Gm in most cases and effective blood levels may be maintained by the administration of 1 Gm only every 6 to 8 hr. About 85 per cent of sulfamerazine is bound to plasma proteins. The concentration in the tissues is 50 to 75 per cent of that in the plasma. Very little acetylation of sulfamerazine occurs and the tendency to renal tubular damage and calculus formation is less than with sulfadiazine.

Succinylsulfathiazole (Sulfasuxidine, 2-N[4]-succinylsulfanilamidothiazole) and *phthalylsulfathiazole* (Sulfathalidine, 2-N[4]-phthalylsulfanilamidothiazole) are poorly absorbable from the intestinal tract and are used primarily, therefore, for the suppression of bacterial growth in the intestine. They are usually employed in the preparation of patients for bowel surgery or in the treatment of bacillary dysentery. In the latter disease these agents are generally less effective than sulfadiazine or sulfamerazine.

Gantrisin (3,4-dimethyl-5-sulfanilamidoisoxazole) is more soluble than any of the sulfonamide compounds described above. It is absorbed rapidly from the gastrointestinal tract. About 30 to 35 per cent of the drug is acetylated; this derivative is much more soluble in water than the other sulfonamides in clinical use. The drug is distributed only in the extracellular water of the body and does not penetrate cells. Because of this, the administration of the same quantity of drug will yield a plasma concentration of Gantrisin three times that for sulfanilamide and about twice that for sulfadiazine and sulfamerazine. The clinical effectiveness of Gantrisin is of the same order as that of sulfadiazine. Although smaller quantities were at first thought adequate to produce effective blood levels, more recent experience has suggested that the initial and subsequent doses should be of about the same magnitude as those of sulfadiazine.

Sulfamylon (4-aminomethylbenzenesulfonamide) and *Sulfacetamide* (N-acetylsulfanilamide) are useful in topical treatment of wound and ocular infections.

Elkosin (6-sulfanilamido-2,4-dimethylpyrimidine) is very soluble in urine and favorable results have been reported from its use in urinary tract infections.

Sulfamethoxypyridazine (3-sulfanilamido-6-methoxypyridazine, Kynex) is well absorbed from the gastrointestinal tract and is excreted slowly in the urine. It penetrates the cerebrospinal fluid well and has antibacterial activity about equal to that of sulfadiazine. The administration of a single dose of 3 Gm produces a maximum blood level of 25 mg per 100 ml and the drug may be demonstrable in the urine for as long as 10 to 14 days after a single dose. About 50 per cent of the drug in the urine and 10 to 15 per cent of that in the blood is acetylated. A dose of 1 Gm every 48 hr produces blood levels of 5 to 12.5 mg per 100 ml. Sulfamethoxypyridazine is most useful for prolonged therapy or prophylaxis. The dose recommended for therapy is 1 Gm initially and 0.5 Gm every 24 hr. When higher blood levels are required the dosage can be raised to 2 Gm followed by 1 Gm daily. A weekly dose of 30 mg/kg body weight

has been suggested for prophylaxis against streptococcal infections in rheumatic subjects Blood levels should be determined if therapy is continued for more than 1 week This is mandatory in patients with impaired renal function

Diaminodiphenylsulfone and *Promizole* are sulfones which possess potent antibacterial activity but have the disadvantage of a tendency to cause granulopenia and hemolytic anemia Their use has been restricted largely to the treatment of tuberculosis and leprosy and is discussed in the chapters on these diseases

ANTIBIOTICS

The development of antibiotics for the treatment of infections constitutes one of the most important advances in modern medicine Although a very large number of antimicrobial substances have been isolated from all types of microorganisms plants animal tissues and other sources many have proved too unstable or too toxic to have a clinical application Among those which are clinically useful are penicillin, streptomycin Aureomycin Chloromycetin Terramycin Achromycin erythromycin bacitracin polymyxin and neomycin

Properties of Antibiotics

Antibiotics are chemical substances which are produced by microorganisms and have the capacity to inhibit the growth of and even to destroy bacteria and other microorganisms They are characterized by certain distinct physical chemical and biologic properties which make them ideal potential chemotherapeutic agents for the treatment of infection These properties can be described briefly

1 Antibiotics are selective in their effect on different microorganisms being specific in their action not only against genera and species but even against strains and individual cells Some of these agents act mainly on gram positive bacteria while others inhibit only gram negative ones Others affect alike various types of bacteria regardless of their tinctorial properties Some have no effect upon fungi while others although too toxic to be clinically useful at present, are actively fungistatic Certain antibiotic agents are effective against rickettsiae and a few of the larger viruses The variations in the action of these drugs upon different bacteria and other parasites are both qualitative and quantitative this has led to the development of the concept of an antibiotic spectrum which records the selective action of a given antibiotic upon a number of representative bacteria and other microorganisms

2 The antibiotic agents represent a large number of chemical compounds ranging from simple substances containing only carbon hydrogen and oxygen to more complex forms which contain nitrogen sulfur and even chlorine They vary greatly in chemical structure

3 Certain microorganisms are capable of producing more than one antibiotic *Streptomyces griseus* for example produces streptomycin and mannosidostreptomycin the antifungous agent actidione and the antitrichomonas substance streptocin

4 Some antibiotics are produced by several different organisms Thus various penicillins are formed by different strains of *Penicillium*

5 Salts and serum proteins among other factors may reduce the effectiveness of an antibiotic by neutralizing adsorbing or inactivating it

6 Some antibiotics penicillin for example are rapidly destroyed by various bacteria whereas others such as streptomycin are highly resistant to microbial action

7 The mode of action of antibiotics upon organisms varies Some interfere with growth and cell division Others affect microbial respiration or the utilization of essential metabolites

8 Antibiotics vary greatly in their toxicity for animals and man

9 Most antibacterial agents are potentially capable of eliciting various types of hypersensitivity reactions in patients to whom they are administered

10 Bacteria sensitive to an antibiotic may gradually develop resistance after contact for varying periods Different antibiotics vary greatly in this respect With streptomycin rapid development of insensitivity is common penicillin allows only gradual development of resistance of very few sensitive bacteria

11 The application of antibiotics in the chemotherapy of infections may produce pronounced alterations in the normal bacterial flora of the body especially in the mouth pharynx, and gastrointestinal tract

Modes of Action of Various Antibiotics

Penicillin in low concentrations is bacteriostatic large quantities produce a bactericidal effect Organisms are killed only if they are exposed to the drug while they are in an active phase of multiplication Although the mode of action of penicillin has not been completely elucidated several mechanisms have been suggested The drug combines reversibly with cellular constituents essential for division Derangements of nucleic acid synthesis with decreased formation of ribonucleic acid and desoxyribonucleic acids have also been observed Studies of the binding of the antibiotic agent by organisms have indicated that the more sensitive a strain is the more penicillin is bound without relation to the metabolic state of the bacteria Once bound the drug has the same toxicity for all organisms regardless of their sensitivity

oral administration of 12 to 15 Gm sodium bicarbonate per day With the increase in solubility of the sulfonamide in the urine the excretion of the drug is simultaneously more rapid The concentration is thus lowered in the blood and this makes necessary the administration of larger quantities in order to raise the blood level to the point of maximal effectiveness In many clinics therefore alkalinization of the urine is not carried out Another method of preventing precipitation in the urinary tract is to administer two or three sulfonamides concomitantly since the solubility of each is independent of the presence of the others This however may have a disadvantage since in vitro at least combinations of sulfonamides often exhibit much less antibacterial activity than the drugs used singly Lower nephron nephrosis a rare complication of sulfonamide therapy usually occurs in patients who have taken one of these drugs in the past it may follow the ingestion of as little as 1 Gm of the agent It is a totally unpredictable and unavoidable accident for which there is no specific therapy Another rare but serious manifestation of sulfonamide toxicity is acute hemolytic anemia This may develop within 48 hr of therapy and is manifested by a rapid fall in the number of erythrocytes rising icterus high fever and hemoglobinuria Drug administration should be discontinued at once and blood transfusions given

Sulfadiazine (2 sulfanilamidopyrimidine) is absorbed from the gastrointestinal tract slowly and incompletely Excretion of this agent by the kidney occurs more slowly than with some of the other sulfonamides It may be recovered in pleural synovial pericardial peritoneal and edema fluids the tissue concentration being 60 to 75 per cent of that in the plasma About 50 per cent of the drug is bound to protein but there is no correlation between this and the clinical effectiveness Only small amounts of the agent are acetylated Sulfadiazine appears in the urine in both the free and acetylated forms Neither is very soluble and crystalluria is common For most types of systemic infection in adults sulfadiazine is administered in a dose of 4 to 6 Gm per day following an initial dose of 4 Gm In young children 0 065 to 0 1 Gm per lb of body weight per 24 hr usually produces an adequate effect the initial dose should be about one half of this quantity

Sulfamerazine (4 methyl 2 sulfanilamidopyrimidine) is absorbed more rapidly and completely from the gastrointestinal tract than sulfadiazine For these reasons the loading dose need be only 2 Gm in most cases and effective blood levels may be maintained by the administration of 1 Gm only every 6 to 8 hr About 85 per cent of sulfamerazine is bound to plasma proteins The concentration in the tissues is 50 to 75 per cent of that in the plasma Very little acetylation of sulfamerazine occurs and the tendency to renal tubular damage and calculus formation is less than with sulfadiazine

Succinylsulfathiazole (Sulfasuxidine 2 N[4] succinylsulfanilamidothiazole) and *phthalylsulfathiazole* (Sulfathalidine 2 N[4] phthalylsulfanilamidothiazole) are poorly absorbable from the intestinal tract and are used primarily therefore for the suppression of bacterial growth in the intestine They are usually employed in the preparation of patients for bowel surgery or in the treatment of bacillary dysentery In the latter disease these agents are generally less effective than sulfadiazine or sulfamerazine

Gantrisin (3 4 dimethyl 5 sulfanilamidoisoxazole) is more soluble than any of the sulfonamide compounds described above It is absorbed rapidly from the gastrointestinal tract About 30 to 35 per cent of the drug is acetylated this derivative is much more soluble in water than the other sulfonamides in clinical use The drug is distributed only in the extracellular water of the body and does not penetrate cells Because of this the administration of the same quantity of drug will yield a plasma concentration of Gantrisin three times that for sulfanilamide and about twice that for sulfadiazine and sulfamerazine The clinical effectiveness of Gantrisin is of the same order as that of sulfadiazine Although smaller quantities were at first thought adequate to produce effective blood levels more recent experience has suggested that the initial and subsequent doses should be of about the same magnitude as those of sulfadiazine

Sulfamylon (4 aminomethylbenzenesulfonamide) and *Sulfacetamide* (N acetylsulfanilamide) are useful in topical treatment of wound and ocular infections

Elkosin (6 sulfanilamido 2 4 dimethylpyrimidine) is very soluble in urine and favorable results have been reported from its use in urinary tract infections

Sulfamethoxypyridazine (3 sulfanilamido 6-methoxypyridazine Kynex) is well absorbed from the gastrointestinal tract and is excreted slowly in the urine It penetrates the cerebrospinal fluid well and has antibacterial activity about equal to that of sulfadiazine The administration of a single dose of 3 Gm produces a maximum blood level of 25 mg per 100 ml and the drug may be demonstrable in the urine for as long as 10 to 14 days after a single dose About 50 per cent of the drug in the urine and 10 to 15 per cent of that in the blood is acetylated A dose of 1 Gm every 48 hr produces blood levels of 5 to 12 5 mg per 100 ml Sulfamethoxypyridazine is most useful for prolonged therapy or prophylaxis The dose recommended for therapy is 1 Gm initially and 0 5 Gm every 24 hr When higher blood levels are required the dosage can be raised to 2 Gm followed by 1 Gm daily A weekly dose of 30 mg/kg body weight

therapeutic agents Streptomycin is notorious for inducing resistance Of special theoretic interest is the emergence of a state of dependence upon streptomycin *as a growth factor* In these instances the status of the antibiotic seems to have changed from that of an antibacterial agent to that of a bacterial vitamin This phenomenon has been observed with coliform bacteria gonococci and tubercle bacilli

The development of drug resistance may be the result of selective survival of naturally occurring variants or possibly the production of mutants in the culture The presence of the chemotherapeutic agent does not increase the rate of appearance of these insensitive forms which are at first in such a minority that they escape detection However as the growth of susceptible bacteria is inhibited *the resistant variants multiply and* eventually outnumber the susceptible ones

The acquisition of drug resistance is at present being observed more and more frequently in vivo One of the most important problems in this respect is the increasing number of staphylococci which are insensitive not only to penicillin but also to some of the so called broad spectrum antibiotics (see p 839)

Streptomycin treatment very commonly induces resistance in organisms Some of the bacteria involved in urinary tract infections and *Hemophilus influenzae* for example may become totally insensitive to streptomycin within 3 or 4 days after the initiation of therapy An increasing number of bacteria both gram negative and gram positive have been shown to develop varying degrees of lack of susceptibility to Aureomycin Chloromycetin Terramycin and erythromycin

Organisms which become insensitive to one antibiotic may simultaneously develop resistance to another Thus not infrequently bacteria which lose their susceptibility to Aureomycin simultaneously exhibit insensitivity to Terramycin Chloromycetin and Achromycin The development of neomycin resistance is quite readily associated with a significant loss of sensitivity to streptomycin The reverse does not occur so regularly

Combination of antibiotics may result in a diminution in the speed of emergence of bacterial resistance to any of the drugs in the mixture Organisms exposed to erythromycin alone in vitro rapidly become insensitive if in contact with both erythromycin and penicillin or erythromycin and streptomycin insensitivity to all the agents develops at a much lower and slower rate Clinical experience indicates that the emergence of resistance in the tubercle bacillus to streptomycin may be considerably delayed by the simultaneous administration of para aminosalicylic or isonicotinic acid hydrazide

DETERMINATION OF DRUG CONCENTRATIONS IN BODY FLUIDS

Knowledge of the absorption distribution and excretion of chemotherapeutic agents is of the greatest importance in determining methods of clinical use Sulfonamide and Chloromycetin concentrations in various body fluids can be determined chemically using colorimetric techniques For most of the antibiotics however there is no means of chemical analysis and much more tedious and inaccurate *bioassay methods are required The general* plan of these procedures is to test the body fluid blood urine spinal fluid etc for capacity to inhibit growth of a standard test tube bacterium as compared with the effect of known concentrations of the chemotherapeutic agent

In clinical practice there is relatively little point in *determining the concentration of antibiotic in* body fluids because of the wide margin of error in the bioassay method and because of delay before the results are known Blood levels are sometimes helpful during sulfonamide therapy to warn the clinician when toxic levels are being approached

PENICILLIN

The term *penicillin* was applied by Fleming to a substance produced by *Penicillium notatum* which exhibited inhibitory effect on the growth of certain pathogenic bacteria Subsequent investigation disclosed that the mold produces several penicillins closely related chemically and in biologic activity At the present time only one of them is used extensively in clinical medicine It is called penicillin G or benzyl penicillin or penicillin II The other penicillins have been discarded because of difficulty in manufacture or because they are less effective Penicillin G has been prepared synthetically but the process is very complex consequently the entire supply is still produced by fermentation methods

Now that the drug is available in the form of a *pure crystalline material it would seem preferable* to express dosage in terms of weight but because of established clinical usage it will be difficult to break away from the original arbitrary unit system based upon bioassay Actually 1 000 units is equal to 0 6 mg penicillin G

Penicillin may be administered by several routes orally intramuscularly subcutaneously intravenously or by inhalation It has also been applied topically Application to the skin especially if preparations dissolved in oily bases are employed is to be avoided wherever possible because the degree of sensitization to the drug produced by this type of therapy is very high The procaine salt of the antibiotic is probably the most extensively used preparation because absorption is slowed and

The exact mechanisms by which *streptomycin* inhibits bacterial growth have not yet been elucidated This antibiotic is known however to interfere with normal cell division without disturbing cell growth Streptomycin appears to be capable of disintegrating the cell wall of *Klebsiella pneumoniae* It has been suggested that the drug interferes with the formation of adaptive enzymes in inhibiting respiration Studies of the mode of action of streptomycin on *Mycobacterium tuberculosis* indicate that only the oxidation of long chain fatty acids is sensitive to the antibiotic Some of the metabolic effects of this antibacterial agent are not related to its cytotoxic activity

Chloromycetin affects the amino acid metabolism of sensitive organisms It drastically inhibits protein synthesis as little as 1 to 5 gamma of the drug depresses protein synthesis by *Micrococcus pyogenes* (also called *Staphylococcus pyogenes* through established medical usage) as much as 90 per cent

The mode of action of the tetracycline compounds chlortetracycline (Aureomycin) oxytetracycline (Terramycin) and tetracycline itself (Achromycin) is probably the same for all the derivatives since they exert approximately the same qualitative antibacterial effects and produce cross resistance These agents are bacteriostatic and do not kill organisms directly unless the ratio of concentration of antibiotic to the initial number of bacterial cells is very high The tetracyclines affect oxidation and fermentation in a number of organisms There is strong evidence that they derange nucleic acid formation and protein synthesis

Very little is known about the mechanism of action of other antibiotic agents Phenylalanine or pantothenate causes striking reversal of erythromycin activity Polymyxin E has been found to combine with and probably disorganize the structures responsible for the maintenance of osmotic equilibrium within the cell wall

Testing Organisms for Sensitivity to Various Antibiotics

The sensitivities of bacteria to various chemotherapeutic agents are usually determined by bacteriologic techniques The most accurate method for use in the routine bacteriology laboratory involves inoculation of the organism into culture medium in test tubes containing serial dilutions of the drug After a suitable period of incubation the lowest concentration of antibiotic which inhibits growth of the bacteria is expressed as the sensitivity A more rapid but less accurate method of determining sensitivity involves the use of filter paper disks which have been infiltrated with a known quantity of drug These disks are placed on the surface of blood agar plates on which the organism undergoing test has been streaked The smallest quantity of antibiotic around which inhibition of growth is present is the level of sensitivity of the bacteria This procedure is relatively crude and although useful in clinical practice for the rapid determination of relative sensitivities of organisms does not take the place of the test tube serial dilution technique Wide ranges of values may be obtained for the minimal inhibiting concentrations of any one antibiotic for any given bacterium depending on the method of testing used

Determinations of the sensitivity of an organism to chemotherapeutic agents may be helpful in the management of an infectious disease and clinical laboratories should always be able to carry out such tests reliably They are not necessary in all or even in a majority of cases furthermore there is only a rough correlation between clinical response to a chemotherapeutic agent and the result of the sensitivity test Nevertheless the procedure may be invaluable in indicating which therapeutic agent to employ and the general level of dosage required For example penicillin sensitivity tests on the causative organism should be done in all cases of bacterial endocarditis and systemic infections with *Staphylococcus aureus* or whenever a serious infection is not responding satisfactorily to the treatment given

Resistance of Bacteria to Antibiotics

Each chemotherapeutic agent has a certain range of effectiveness among the various classes of microorganisms Presumably the principal determining factor in this is whether the enzyme system affected by the drug is essential to the existence of a given parasite Another factor is the elaboration by the parasites of substances which inactivate the chemotherapeutic agent For example the *Pseudomonas* group of bacteria which are *naturally resistant to* penicillin produce a penicillinase which when added to a culture medium will inhibit the bacteriostatic action of that drug for organisms normally susceptible to it Some naturally resistant strains of *Staphylococcus* also have been found to elaborate penicillinase Certain bacteria whose growth is not inhibited by sulfonamides synthesize comparatively large amounts of PABA

Acquired Resistance of Bacteria Bacteria growing in the presence of chemotherapeutic agents may exhibit an alteration in susceptibility by virtue of which they become able to grow in concentrations of drug which originally would have suppressed them completely This kind of change can occur within the animal body as well as in the test tube The rapidity with which it develops varies with different bacterial strains and with different chemo

sorbed from the gastrointestinal tract In the treatment of bacterial enteritis—bacillary dysentery for example—the antibiotic is usually administered orally in a dose of 0 25 to 0 5 Gm every 6 hr For systemic infections it is injected intramuscularly at 6 or 12 hr intervals When treatment is required for only a few days 3 or 4 Gm may be given per day large doses should be avoided wherever possible however because of the increased danger of eighth nerve injury Solutions for injection should contain no more than 0 5 Gm per ml since higher concentrations often produce considerable pain Intrathecal administration may be important in the management of meningitis due to organisms susceptible to this antibiotic agent The quantity instilled intraspinally should be dissolved in 10 ml physiologic saline solution this is administered every 12 or 24 hr for 2 or 3 days depending on the clinical situation

Specific indications for the use of streptomycin in various diseases are described in other chapters of this book

CHLORTETRACYCLINE (Aureomycin)

This antibiotic is a product of *Streptomyces aureofaciens* It is a remarkable antibacterial agent because of its wide range of activity encompassing not only many gram positive and gram negative bacteria but also the *Rickettsiae* and some of the larger viruses Many strains of *S aureus* and some of the gram negative bacteria like *Proteus vulgaris* and *Pseudomonas* may become rapidly insensitive to the drug Aureomycin is a basic substance but is usually prepared in the form of a hydrochloride which is strongly acid in reaction The dry salt is stable but in solution it deteriorates rapidly especially if the pH is above 6 Aureomycin is so unstable in the presence of body fluids and in bacteriologic media that definitive studies on its absorption fate and excretion have been difficult to obtain Absorption from the gastrointestinal tract is rapid but inefficient as a result of destruction of the antibiotic by intestinal contents After a single oral dose it can be demonstrated in the urine within 15 min and for as long as 24 hr Concentration in the plasma falls rapidly below detectable level suggesting the possibility of localization and gradual release in some tissue or body fluid Only a small proportion of the quantity injected parenterally can be demonstrated in the urine Aureomycin diffuses into the spinal fluid but in smaller amounts than into the plasma Concentrations of more than 0 2 per cent are very irritating because of the acidity and can cause marked local inflammatory changes with necrosis Subcutaneous and intramuscular injections therefore are not practical Intravenous administration of buffered solutions is possible but there is some risk of phlebitis at the site of injection When the drug is given by mouth nausea and vomiting occur occasionally Attempts to overcome this gastric irritation by the administration of aluminum hydroxide lead to a reduction of the serum concentration of Aureomycin by 80 per cent or more these two agents should not be used together The ingestion of milk or food reduces gastric irritation without altering plasma levels of the drug Mild diarrhea associated with loose bulky stools may be caused by the local irritation or alteration in the bacterial flora of the intestinal tract due to the antibiotic

The dose range of the antibiotic is from 1 to 6 Gm per day given in divided doses at 6 or 8 hr intervals in most clinical infections quantities larger than 1 Gm per day are probably not necessary The dose for intravenous administration is about one third to one fifth as large as that given by mouth

CHLORAMPHENICOL (Chloromycetin)

The initial preparations of Chloromycetin were obtained from cultures of *Streptomyces venezuelae* The drug has been isolated in pure crystalline form and synthesized There is no difference in the antibacterial activity of the synthetic and the natural products The presence of an NO group makes possible a colorimetric method of determination similar to that used for the sulfonamides

Chloromycetin is a white neutral crystalline powder which is stable in the dry state In solutions ranging in pH from 2 to 9 it is stable at room temperature for at least 24 hr It is highly insoluble in water—approximately 0 25 per cent soluble at room temperature—but it is soluble in propylene glycol up to 15 per cent

Most treatment with Chloromycetin is carried out by the oral route although preparations are available for intramuscular or intravenous injection The demonstration that this agent may on occasion depress the bone marrow suggests caution in its administration The drug is rapidly absorbed from the gastrointestinal tract appearing in the blood within a few minutes The maximal concentration occurs at the end of 2 hr but some may still be found after 16 or 24 hr About 80 per cent of the quantity administered orally can be demonstrated in the urine by the colorimetric method however only about 15 per cent is still active according to bioassay Inactivation appears to be due to conjugation with glucuronic acid

A large number of organisms are susceptible to Chloromycetin Although it is active *against some* types of gram positive bacteria it is most effective against the rickettsiae and gram negative organisms *S aureus* coliform bacilli and *other enteric organ*

detectable blood levels may be present for as long as 24 hr The addition of aluminum monostearate to procaine penicillin may allow detectable blood levels to be maintained for as long as 48 to 72 hr Solutions of crystalline penicillin G in physiologic saline may be inhaled for the treatment of various acute or chronic pulmonary infections

Among the more recently developed types of penicillin are Bicillin (dibenzylethylenediamine dipenicillin) and penicillin V (phenoxymethyl penicillin) Bicillin may be administered either by mouth or parenterally When given orally however the absorption of this agent is more erratic than that of buffered penicillin G which yields three to six times the penicillin activity of Bicillin The intramuscular injection of Bicillin has the advantage over penicillin G of prolonging the duration of blood levels the administration of 200 000 to 500 000 units may produce a detectable concentration of antibiotic in the blood for as long as 2 weeks Penicillin V differs from G in a single oxygen molecule The free acid and potassium salt are more stable and much less soluble at the pH of gastric juice than is penicillin G Penicillin V is however rapidly dissolved in alkaline solution and is readily absorbed from the upper portion of the small intestine Taken by mouth penicillin V produces higher and more prolonged blood levels than the same quantity of penicillin G The intramuscular injection of penicillin V produces lower blood levels than penicillin G given by the same route

Only about 20 per cent of an orally administered dose of penicillin G is absorbed into the blood stream the remainder being destroyed by gastric acidity and by penicillinase in the lumen of the intestines As a consequence much larger doses are needed for oral than for parenteral therapy Administration of alkalinizing agents with the drug apparently does not increase appreciably the amount absorbed Penicillin should not be given by mouth later than 1 hr before or earlier than 2½ hr after a meal When penicillin is injected subcutaneously or intramuscularly it causes little or no local irritation and is absorbed very rapidly into the blood stream from where it is either excreted by the kidneys or distributed evenly in the plasma and extracellular fluid Normally only minute amounts penetrate into the cerebrospinal fluid *but in the presence of meningeal inflammation* appreciable levels of the drug may be obtained

Penicillin is excreted by the kidneys with great rapidity mainly by a tubular mechanism about 10 per cent being cleared in the glomerular filtrate The renal clearance approximates the total renal blood flow Attempts have been made to delay renal excretion by concurrent administration of substances which compete for available tubular excretory structures Diodrast para aminohippuric acid and Benemid (*p* di *n* propylsulfamyl benzoic acid) retard penicillin excretion to a variable degree Benemid appears to be the most effective in reducing the rapidity of excretion of penicillin the dose is 0 5 Gm four times a day

Penicillin is almost devoid of toxicity in the human being It does produce however a number of untoward effects many of which are due to the development of hypersensitivity These are discussed in detail below

The clinical use of penicillin in treating specific infections is discussed in detail in other chapters of this book

STREPTOMYCIN

Streptomycin is an antibiotic produced by *S griseus* It is active against both gram positive and gram negative organisms the latter being more sensitive than the former This drug is the most powerful of all tuberculostatic agents

Dihydrostreptomycin is a derivative of streptomycin which is produced by catalytic hydrogenation It has been used in place of streptomycin because it was believed to produce less neurotoxicity However damage to the auditory nerve following dihydrostreptomycin therapy is about as frequent as that following streptomycin provided full doses are employed Streptomycin tends to affect the vestibular portion, while dihydrostreptomycin produces most of its damage in the cochlear portion of the eighth nerve There is evidence that dihydrostreptomycin is as effective as streptomycin gram for gram in the treatment of tuberculosis and all other infections susceptible to the action of streptomycin The dihydro derivative appears to cause fewer reactions of hypersensitivity than streptomycin and can be administered to patients who are intolerant of the latter

Streptomycin is a basic substance and is usually prepared in the form of a hydrochloride or sulfate which is readily soluble in water

Streptomycin salts or dihydrostreptomycin are readily soluble in water The drug is poorly absorbed from the gastrointestinal tract When injected parenterally streptomycin is distributed evenly in extracellular body fluids but very little if any penetrates the blood–spinal fluid barrier *unless meningeal inflammation is present* After a single intramuscular injection approximately 80 per cent of the antibiotic appears in the urine over a period of 24 hr Renal excretion appears to be largely by filtration

There are three routes of administration intramuscular topical and oral Streptomycin is given by mouth when a local effect in the intestinal tract is desired but this route is of no value in the treatment of systemic infections because so little is ab

rapidly Despite the relatively short period of time during which this agent has been used an incidence of 25 per cent of erythromycin insensitive strains of *S aureus* has already been reported from one clinic Because of this it is probably best, in clinical practice not to administer erythromycin alone penicillin or streptomycin should be given concurrently

BACITRACIN

Bacitracin is a polypeptide antibiotic produced by a strain of *Bacillus subtilis* The bacterial spectrum resembles that of penicillin The drug is soluble in water or physiologic saline solution It is most frequently applied topically in various types of ointment For systemic administration it is usually dissolved in 2 per cent Novocain solution in physiologic saline solution

Very little bacitracin is absorbed from the gastrointestinal tract although it inhibits the growth of many bacteria in the bowel including clostridia and gram positive cocci The antibiotic appears in the blood and tissues but very little diffuses into the cerebrospinal fluid after intramuscular injection The renal clearance of the drug is low and approximates the glomerular filtration rate Bacitracin is excreted slowly it is unlike penicillin in that plasma concentrations may remain elevated for several hours

Bacitracin has its greatest clinical application in the topical therapy of infections due to *S aureus* and other gram positive bacteria particularly those resistant to other antibiotics The large number of strains of micrococci insensitive to all the commonly used chemotherapeutic agents occasionally necessitates consideration of parenteral administration of bacitracin in systemic disease The intramuscular dose is 15 000 to 20 000 units given four times a day Larger quantities increase the risk of serious renal damage Careful attention must be given to the development of nephrotoxic manifestations if kidney dysfunction becomes appreciable the drug should be discontinued

POLYMYXIN (Aerosporin)

Polymyxin is a polypeptide antibiotic obtained from *Bacillus polymyxa* The principal effect is upon gram negative bacilli for which it is one of the most potent chemotherapeutic agents available strains of *Proteus* are however resistant The drug can be administered intramuscularly at intervals of 8 or 12 hr the total daily dose being 0 2 to 0 5 Gm It is not absorbed from the bowel but it eliminates sensitive organisms from the intestinal flora Following parenteral use it disappears from the blood quickly It does not pass into the cerebrospinal fluid and cannot be detected in the bile or in the urine in biologically active form Considerable limitation of usefulness arises from its toxicity for the kidney this becomes evident usually on about the fourth or fifth day of treatment in a significant proportion of patients There may be only proteinuria or oliguria, or nitrogen retention may supervene Some preparations of the antibiotic have been found to be relatively free of nephrotoxicity Although not detectable in man antidiuretic activity for animals has been demonstrable in some preparations of polymyxin Because of the danger of renal damage this chemotherapeutic agent should be employed only when others are ineffective and when the patient s life is in jeopardy Impressive clinical results have been produced in some cases of *Pseudomonas aeruginosa* bacteremia and in meningitis due to the same organism

NEOMYCIN

Neomycin is an antibiotic derived from a strain of *Streptomyces* closely related to *Streptomyces fradiae* It is a basic compound heat stable and resistant to the action of acid (pH 2) at the temperature of boiling water It is bactericidal in vitro against a wide variety of gram negative and gram positive organisms There is some indication that it is the most effective chemotherapeutic agent in the treatment of infections due to *Pr vulgaris* The drug has been administered by oral and parenteral routes Absorption from the intestinal tract is relatively poor The result of 2 Gm given by mouth every 6 hr is a concentration of neomycin in the blood one-eighth as high as that which follows the intramuscular injection of only 0 5 Gm every 6 hr The usual oral dose of neomycin is 2 Gm in divided doses per day The antibiotic may also be administered intramuscularly the daily dose is 1 to 2 Gm

Although the in vitro antibacterial effectiveness of neomycin is impressive its clinical usefulness is sharply limited by high toxicity Kidney and eighth nerve damage occur in a significant number of patients In view of these untoward effects neomycin should *never* be the first drug employed in the treatment of any infection It should be reserved for those diseases in which no other antibiotic is effective and the infection threatens life The magnitude of the risk of renal or auditory nerve injury must always be weighed against that of the untreated infection If used critically and intelligently neomycin may occasionally be life saving

NOVOBIOCIN

Novobiocin (Cathomycin, Streptonivicin Albamycin Cardelmycin) is elaborated by both *Strepto*

isms are known to become resistant to this antibiotic

Aside from the mild gastrointestinal irritation produced by Chloromycetin the most serious untoward effect which results is depression of the bone marrow Granulopenia develops first and may be followed by aplastic anemia if administration of the drug is continued this is rare The other complications of Chloromycetin therapy are discussed below

OXYTETRACYCLINE (Terramycin)

Terramycin is an antibiotic produced by *Streptomyces rimosus* It is very closely related chemically to Aureomycin This agent is available for clinical use in the form of a hydrochloride It may be administered orally or intravenously and is relatively stable over a wide range of temperature and pH

The most commonly used form of Terramycin is the capsule of the crystalline hydrochloride salt This is available in 50 100 and 250 mg doses for oral use Intravenous injection of this antibiotic should be reserved for instances of severe illness or for cases in which it cannot be taken by mouth Solutions of Terramycin must be properly buffered and in no circumstances should unbuffered drug be given for any purpose

Terramycin is absorbed rapidly from the gastrointestinal tract No significant difference is present in the plasma concentration when the agent is given in the fasting or nonfasting state A single oral dose may produce detectable concentrations in the blood for as long as 24 hr When 250 mg of the drug is given at 6 hr intervals blood levels are usually in the order of 5 to 10 μg per ml throughout the 24 hr period Intravenous injection produces serum levels ranging between 5 and 10 μg per ml at the end of 1 hr and from 1 to 5 μg per ml after 12 hr

The clinical applications of Terramycin are practically the same as those for Aureomycin There is very little difference in antibacterial activity between these two agents

TETRACYCLINE (Achromycin)

Achromycin is closely related chemically to both Aureomycin and Terramycin It is essentially the skeleton structure of these two antibiotics and is prepared synthetically In vitro tests indicate that the biologic activity of Achromycin is equal to that of Aureomycin and Terramycin It appears that Achromycin is useful in the same infections as are known to respond favorably to either Aureomycin or Terramycin The incidence of side reactions such as nausea vomiting and diarrhea is said to be lower following the use of Achromycin than has been observed with the other related drugs The development of bacterial resistance to Achromycin is accompanied by simultaneous loss of sensitivity to other agents

Achromycin is stable in solution maintaining its activity in solution at 37 C for at least 7 days The drug is available in the form of the crystalline hydrochloride in capsules as a dispersible powder and for intravenous use Intravenous therapy should be employed only in patients who are unable to take medication by mouth The average adult dose is 500 mg intravenously at 12 hr intervals This dosage may be increased to a maximum of 500 mg every 6 hr For oral treatment a dose of 1 to 2 Gm divided into four doses per day is usually adequate

ERYTHROMYCIN (Ilotycin)

Erythromycin is an antibiotic elaborated by *Streptomyces erythreus* It has been produced in crystalline form as a basic compound It is soluble only to the extent of 2 mg per ml in water but it is highly soluble in alcohols and in a number of other organic solvents The drug retains its activity in solution at 4 C for at least 8 weeks at room temperature there is some deterioration during the first week but not for the next 2 months whereas at 37 C decrease of antibacterial activity begins to appear on the fourth day and continues progressively thereafter

The usual route of administration of erythromycin is by mouth the drug is absorbed from the intestinal tract There is a rough correlation between maximal blood level and the dose of antibiotic ingested Peak serum concentrations appear 1 to 2 hr after ingestion of a dose and decline rapidly so that the agent is no longer demonstrable after 4 to 6 hr Only small amounts are recovered from the urine

Gram positive organisms including *S aureus* are highly sensitive to erythromycin being inhibited on the average by concentrations of less than 1 μg per ml

In clinical practice the use of erythromycin should be restricted to the treatment of infections due to gram positive organisms Since penicillin is so highly effective in pneumococcal and beta hemolytic streptococcal diseases and no penicillin resistant strains of these bacteria have yet been discovered erythromycin is not the drug of choice in these infections Strains of *S aureus* which are insensitive to all other antibiotics may be highly susceptible to erythromycin This chemotherapeutic agent is therefore most valuable in the management of disease produced by staphylococci or other penicillin resistant gram positive organisms

Bacteria exposed to erythromycin either in vitro or in vivo become resistant to the drug quite

fying agent has been suggested The development of bacterial resistance to the drug has not been noted

The infections of the urinary tract which respond most favorably to therapy with nitrofurantoin are the acute and uncomplicated ones Infections produced by E coli are the most easily eradicated by this agent Those due to *Ps aeruginosa* are totally unaffected and infections caused by *A aerogenes* occupy an intermediate position *Pseudomonas aeruginosa* may appear in the urine for the first time during a course of treatment with nitrofurantoin Although the drug has been said to be most active against *Proteus* infection the results are quite variable Not infrequently this organism is only temporarily suppressed and reappears after cessation of therapy

Nitrofurantoin is relatively nontoxic Nausea with or without vomiting is the commonest untoward reaction Various types of rashes have been described Although it is known to suppress spermatogenesis in animals when given in large quantities this effect has not been observed in man

TUBERCULOSTATIC DRUGS

Although streptomycin is effective in the treatment of all types of tuberculosis the use of this agent alone leaves much to be desired in the way of maximal antibacterial effect as well as in preventing the emergence of drug resistant strains of *M tuberculosis* For these reasons attempts have been made to develop other compounds possessing tuberculostatic activity which might be employed alone or might be given concurrently with streptomycin Two such agents are para aminosalicylic acid and isonicotinic acid hydrazide

Para aminosalicylic Acid (PAS) Para aminosalicylic acid is a white crystalline powder It is sparingly soluble in water but is easily dissolved in the form of its sodium salt This agent has a bacteriostatic effect in vitro against many strains of *M tuberculosis* even those which have become streptomycin resistant The antibacterial activity is not inhibited by serum or sodium salicylate but is partially decreased by PABA

Para aminosalicylic acid and its sodium salt when given orally are rapidly absorbed and quickly excreted It is necessary to give the drug frequently in order to reach and maintain adequate blood levels A single dose produces maximal serum concentration within 30 to 60 min of administration thereafter there is a gradual fall so that the agent disappears from the blood in 2 to 3 hr The agent attains high concentrations in the interstitial tissues of the pulmonary alveoli in the liver and in the kidney It also diffuses into the cerebrospinal fluid and the pleural cavity The quantities are smaller in tuberculous cavitation than in normal lung Para aminosalicylic acid is almost entirely excreted by the kidney in unchanged or acetylated forms

Para aminosalicylic acid is usually given orally Since considerable gastric irritation may result from the large quantities necessary the concurrent administration of various types of alkali or milk is advisable Various mixtures containing flavoring and alkaline compounds have been employed Preparations for intravenous use are also available these should be reserved for patients in whom severe gastric distress prohibits oral use or for those in coma The usual quantity given by mouth is 8 to 12 Gm per day in divided doses Although it has been reported that PAS alone may be effective in the treatment of mild tuberculous infections it is best to give this agent together with streptomycin The details of this type of treatment are described in Chap 141 Tuberculosis Tubercle bacilli may become resistant to PAS if this drug is used alone Combination with streptomycin delays remarkably the speed of emergence of resistance of the organisms to both agents The other advantage of such combined therapy is the additive tuberculostatic action of the two drugs

The most common toxic effects produced by PAS are nausea vomiting and burning epigastric distress Diarrhea occurs occasionally Toxic damage to the liver and potassium deficiency have been recorded Prolongation of the clotting time of the blood has been noted in patients to whom large quantities (30 Gm per day) have been given the administration of synthetic vitamin K prevents the onset of this prothrombin deficiency and cures it if it has appeared Occasionally tinnitus and reduction in the acuity of hearing may develop they usually disappear rapidly after cessation of treatment

Isonicotinic Acid Hydrazide This is the most recently developed drug which has been used in the therapy of tuberculosis Of all the tuberculostatic agents isonicotinic acid hydrazide has the highest activity in vitro It is not effective against organisms other than *Mycobacteria*

Isonicotinic acid hydrazide is administered orally as a rule and is almost completely absorbed from the digestive tract From one half to three quarters of the amount ingested is recovered from the urine in 24 hr and not more than 5 to 10 per cent appears in the feces The peak serum concentration may occur from 1 to 3 hr after administration and the minimal detectable concentration of 0 4 *µg per ml* persists for 6 to 24 hr This level is higher than that necessary to control tubercle bacilli *in vitro* The drug is well distributed in the various body fluids and is not inactivated by them it is present in sputum urine pleural exudate plasma and cerebrospinal fluid in active form It passes the

myces niveus and *Streptomyces spheroides* It is a dibasic substance the exact chemical composition of which is not known Although the basic compound is insoluble in water and fat solvents, salts formed with metal ions dissolve readily in aqueous solution In vitro the drug inhibits the growth of strains of S *aureus* resistant to penicillin the tetracycline compounds chloramphenicol and erythromycin as well as hemolytic streptococci *Brucella* the pneumococcus the meningococcus *Hemophilus pertussis* *Pasteurella* and *Proteus* There is a marked decrease in antibacterial activity in the presence of serum more than 90 per cent of novobiocin appears to be bound to serum protein The drug is rapidly absorbed from the intestinal tract it may also be given parenterally After two doses of 0 5 Gm each given 6 hr apart the concentration in the blood ranges between 16 and 128 gamma per milliliter This antibiotic is excreted slowly appreciable amounts are detectable in the serum for 24 hr Novobiocin is excreted in the urine

Most investigators have recommended that the use of novobiocin be restricted to the treatment of staphylococcal infections due to strains which are insusceptible to other antibiotic agents because it has no advantages over other drugs when employed for the eradication of other sensitive organisms However *Proteus* is sometimes sensitive to novobiocin and its use has proved effective in infections produced by strains of this organism insensitive to other antibiotics Staphylococci become resistant to novobiocin rapidly For this reason it should never be administered alone but should be given concurrently with another antibiotic to which the infecting strain is sensitive The usual dose of novobiocin is 0 5 Gm at 6 hourly intervals orally or 1 to 2 Gm in equally divided doses intramuscularly Transient nausea and vomiting and dermatitis have been noted following its administration

NYSTATIN

Nystatin (Mycostatin) is elaborated by *Streptomyces noursei* and has an empirical formula of $C_{46}H_{83}N_{18}$ It is a pale yellow substance insoluble in fat solvents highly soluble in methanol and soluble to the extent of 10 to 20 units per milliliter in water It is poorly absorbed from the gastrointestinal tract High blood levels follow intravenous injection This antimycotic agent is employed for local application in the form of ointments solutions powders suppositories and gels Topical use in the treatment of *Candida* infections of the skin and vagina has been reported to be successful

The usual oral dose of nystatin is 150 mg (500 000 units) three times a day Although an occasional case of disseminated mycotic infection has been treated parenterally with nystatin with reported good results the place of this agent in the therapy of deep seated mycoses still remains to be determined

AMPHOTERICIN

Amphotericin B (Fungizone) has been administered intravenously for cryptococcosis histoplasmosis blastomycosis disseminated moniliasis and coccidioidomycosis The drug is dissolved in 5 per cent glucose to a concentration of 1 mg per 10 ml Solutions maintained at room temperature for over 24 hr must be discarded The drug solution is infused over a period of 6 hr The initial intravenous dose is 0 25 mg/kg body weight this is gradually increased to a maximum of 1 5 mg/kg If therapy is stopped and later reinstituted it is best to begin again with 0 25 mg/kg The duration of treatment varies with the nature of the infection The intramuscular dose is 20 mg dissolved in 2 ml of 5 per cent glucose combined with a local anesthetic given daily In mycotic meningitis the intrathecal injection of 0 5 to 1 mg of the drug dissolved in 5 ml of water every 48 hr has been recommended Increase in NPN chills and fever are the untoward reactions to amphotericin B If the NPN rises above 40 mg per 100 ml therapy should be stopped

NITROFURANTOIN (Furadantin)

Nitrofurantoin [N (5 nitro 2 furfurylidene) 1 aminohydantoin] is an antibacterial agent of value primarily in the treatment of some types of urinary tract infection It is poorly soluble in water The drug is bacteriostatic in high concentrations it is bactericidal Nitrofurantoin is most active against *Escherichia coli* (bactericidal) of intermediate effectiveness against *Aerobacter aerogenes* and completely without effect against *Ps aeruginosa* (*Ps pyocyanea*) The activity of the drug against *Proteus* is variable although many strains are quite sensitive *S aureus* and enterococci are inhibited by low concentrations

Nitrofurantoin is administered orally usually in a dose of 7 to 10 mg per kg (100 to 200 mg four times a day) Useful blood levels cannot be produced The drug is excreted in the urine Within 4 to 6 hr after a maximal clinical dose the concentration in the urine is 25 to 50 mg per 100 ml 8 hr after a dose the levels are low The estimated degree of antibacterial effect in the urine may at times exceed the apparent in vitro solubility at a given pH as predicted from solubility curves in the same medium With highly alkaline urine as is the case in *Proteus* infection the inhibitory effect of nitrofurantoin appears to be depressed for this reason the simultaneous administration of an acidi

individuals to prevent invasion by specific bacteria and has been most successful in protecting against infection by four agents—the beta hemolytic streptococcus the gonococcus the meningococcus and the dysentery bacilli

The administration of penicillin to individuals exposed to invasion by the beta hemolytic streptococcus affords predictable and high order of protection This antibiotic is also highly effective in the prevention of acute gonococcal urethritis A single oral dose of 250 000 units given immediately after contact has been demonstrated to reduce markedly the incidence of this disease Sulfonamides are the most effective agents for the prevention of bacillary dysentery In outbreaks due to sulfonamide insensitive organisms Chloromycetin or the tetracycline compounds may be of value The prevention of all degrees of spread of meningococcal infection is a relatively simple matter because the meningococcus is highly sensitive to sulfadiazine

Chemoprophylaxis in Acutely Ill Individuals The antimicrobial agents have been used extensively for the prevention of bacterial invasion in individuals taken suddenly ill with disorders in which these drugs have no therapeutic effect The primary diseases in which such chemoprophylaxis has been employed are of two types (1) those due to viruses and (2) those which are noninfectious in origin

One of the most common prophylactic uses of the antibiotics is in undefined viral disease of the upper respiratory tract Attempts to prevent secondary infections following the common cold while most desirable have not proved very successful Depending on the antimicrobial agent used certain pathogenic bacteria may be prevented from producing disease in the person with a viral respiratory infection However regardless of the prophylactic program employed invasion by all organisms cannot be eliminated For this reason the etiology of the complications may be altered by chemoprophylaxis but their incidence may be very little if at all changed There is considerable question whether prophylaxis should be used in primary atypical pneumonia or some of the other undefined viral pneumonias since secondary bacterial infection in untreated cases is uncommon In viral influenza the risk of superimposed bacterial disease is greater than in the undefined viral pneumonias and chemoprophylaxis may therefore have more justification

Antibiotics have often been administered in the so-called childhood diseases" to prevent secondary bacterial infection Both penicillin and Aureomycin have been reported to reduce remarkably the number of complications in measles Study of this disease has not however indicated any benefit from the administration of chemotherapeutic agents during the preeruptive or eruptive phase In fact the data have suggested that the incidence of secondary bacterial infections may be higher in patients given an antibiotic than in those not treated Failure of antimicrobial agents to protect against bacterial invasion in "respiratory" poliomyelitis has also been observed Experience in the prevention of superimposed bacterial disease in pertussis has been very disappointing with the use of Terramycin Aureomycin and Chloromycetin

It is common practice in many hospitals to administer antibiotic agents to patients with heart failure coma due to various causes cerebrovascular accidents or shock for the purpose of preventing bacterial infections Despite the wide use of such prophylaxis and the general impression that it is effective no conclusive evidence has been obtained to substantiate its usefulness Since individuals with these conditions are quite susceptible to bacterial invasion they are exposed to the risk of superinfection even if they receive antibiotics

The necessity to catheterize the urinary bladder usually arises as an acute situation Although single catheterizations are attended by a degree of risk of infection of the lower urinary tract the presence of an indwelling tube is almost certain to result in bacterial invasion of the bladder or kidneys or both The sulfonamides usually in a dose of 2 Gm a day have been used for a long time for prophylaxis in this situation The results with these drugs have been variable but in general not very beneficial The use of other antibiotic agents has not significantly altered the situation Two other approaches to this problem have been employed The first is tidal drainage this definitely reduces the risk of infection The other involves increasing the dose of the prophylactic agent to full therapeutic levels for at least 1 week after removal of the catheter because the quantities of drug used for prophylaxis frequently do not prevent bacteria from being present in appreciable numbers despite absence of active infection With cessation of treatment the organisms often multiply and invade the tissues The administration of large doses of a chemotherapeutic agent may eliminate the bacteria before they produce disease

Chemoprophylaxis in Chronic Disease While not all individuals who have had rheumatic fever have residual valvular defects their susceptibility to new episodes of the acute rheumatic state and the risk of cardiac damage make it imperative that everyone who has recovered from this disease be protected against infection by the beta hemolytic streptococcus which is responsible in most instances for recurrences The two agents which have been used most extensively for the prevention of rheumatic fever are sulfadiazine and penicillin (p 863)

It has been estimated that about 25 per cent of cases of subacute bacterial endocarditis follow den

blood brain barrier readily and in cases of meningeal inflammation the quantities in the spinal fluid may be larger than those in the plasma making it extremely valuable in tuberculous meningitis

Cultures of tubercle bacilli acquire resistance to isonicotinic acid hydrazide readily Insensitive strains are recovered from the majority of tuberculous patients who receive this drug alone for from 1 to 2 months There is no cross resistance between isonicotinic acid hydrazide and streptomycin or PAS

Isonicotinic acid hydrazide should be given in combination with streptomycin or PAS Such therapy takes advantage of the additive tuberculostatic effect and also delays considerably the speed of emergence of resistance of the organisms to either agent

Although isonicotinic acid hydrazide is relatively nontoxic a number of untoward effects have been noted following its administration They include drowsiness hyperreflexia tremor of the limbs twitching of the legs difficulty in initiation of micturition nausea abdominal discomfort transient flushing of the face pruritic skin eruptions peripheral neuropathy acute pellagra toxic hepatitis with jaundice temporary arterial vasospasm and mild psychotic reactions

Pyrazinamide and Cycloserine Two of the more recently developed antituberculous agents are cycloserine a fermentation product of *Streptomyces orchidaceus* and pyrazinamide (Aldinamide) a synthetic compound Both have been used in the treatment of human tuberculosis especially that due to organisms resistant to streptomycin or isonicotinic acid or both with promising results Considerably more study is required however before the exact place of these drugs in the therapy of tuberculosis is clearly defined their effectiveness when given in combination with other tuberculostatic agents is under investigation The usual dose of cycloserine is 0 25 Gm given four times daily while that of pyrazinamide is 0 05 Gm/kg/day Although of low toxicity cycloserine has been thought to cause epileptiform seizures changes in personality or definite depression in some patients The most serious untoward reaction to pyrazinamide is acute hepatitis joint pains nervousness palpitation feeling of tightness in the chest febrile reactions and eosinophilia have also been noted

SELECTION OF A CHEMOTHERAPEUTIC AGENT

In the therapy of infections the physician has to choose among an ever increasing number of antibacterial drugs In order to obtain the best results it is essential that he have a working knowledge of the common pathogenic microorganisms While cultural studies are perhaps theoretically desirable in every case they are not always practicable In many instances the etiology can be inferred from the onset and the clinical features of the disease Nevertheless it must be stressed that there are situations in which careful bacteriologic studies are essential to proper treatment and the conscientious physician must take whatever steps are required to obtain experienced bacteriologic help

Even when the etiology of an infectious process is determined selection of an appropriate drug does not follow automatically because there may be wide variations in susceptibility among organisms of the same or related species For example in treating a series of *Proteus* infections it will be found that some strains respond only to streptomycin others to sulfonamides Aureomycin Chloromycetin or even neomycin The cost of the different drugs has to be considered at times since there are very wide differences The nature of the illness may also affect the choice of agent for example an orally administered drug may be unsatisfactory in a patient who is vomiting In critically ill patients is is sometimes wisest to give a combination of drugs until cultural and sensitivity studies reveal which is specifically indicated In such cases cultures should always be taken *before initiation of therapy* If an individual has previously shown hypersensitivity or any other serious reaction to a drug or if he develops such untoward effects during therapy a different agent should be used if possible The approximate order of preference of various antibacterial drugs will not be tabulated as is the usual custom in this chapter Instead the reader is referred to the discussions of the therapy of *specific infections in other parts of this book* where the agents of primary and secondary value in treatment are indicated

THE PROPHYLAXIS OF INFECTION

The chemotherapeutic agents now available offer an excellent means of prophylaxis in many of the infectious diseases Chemoprophylaxis has been used primarily for four purposes (1) to protect healthy individuals either singly or in groups against invasion by specific microorganisms (2) to prevent *secondary bacterial infection in people* acutely ill with diseases for which the antimicrobial agents are not effective (3) to reduce the risk of infection in patients with various types of chronic illness and (4) to inhibit the spread of disease from areas of localized infection or to prevent infection in general in persons who have been subjected to accidental or surgical trauma

Chemoprophylaxis in Healthy Individuals Chemoprophylaxis is most commonly employed in healthy

number of people treated so that even with a con stant incidence the total number of reactions has risen and (3) repeated administration of single or multiple agents so that increasing numbers of people are conditioned to show various manifestations of hypersensitivity when exposed to these drugs

The list of the undesirable effects actually ob served and attributed to therapy with the widely used antimicrobial agents is long and varied and involves most of the organ sy tems Not all the complications have been observed with each of the chemotherapeutic substances and some have been noted with only one of them For purposes of con venience these reactions are discu sed here in rela tion to organ systems In order to conserve space they are presented in tabular form (Table 92)

Table 92 COMPLICATIONS OF CHEMOTHERAPY

I Cutaneous manifestations
  Mostly due to hypersensitivity Occur with all drugs 2 5 to 5 per cent with penicillin Most with procaine salt Lowest (less than 1 per cent) with oral rout
  1 Morbilliform rashes—commonest
  2 Scarlatiniform urticarial vesicular or bullous eruptions
  3 Purpura with or without thrombopenia
  4 Erythema multiforme
  5 Erythema nodosum
  6 Exfoliative dermatitis
  7 Inflammatory reactions at sites of infection
II Oral lesions
  Thirty three different ones de ribed Noted with all antibioti s Commonest with broad spectrum drugs
  1 Dryness burning soreness and itching of mouth and tongue
  2 Ve icular stomatitis
  3 Acute glossitis
  4 Angular stomatitis (cheilosis)
  5 Black or brown tongue
III Other manifestations of hypersensitivity
  1 Fever
  2 Contact dermatitis in nurses and pharmacists handling antibiotics
  3 Angioneuroti edema
  4 Serum sickness reaction id ntical with that fol lowing injection of heterologous serum
  5 Arthus reaction
  6 Acute anaphylactic shock (rare but commonest with penicillin)
  7 ?Polyarteritis nodosa
  8 ?Disseminated lupus erythematosus
IV Gastrointestinal and hepatic complications
  Commonest with broad-spectrum antibiotics
  1 Nausea
  2 Vomiting
  3 Diarrhea due to irritation or transformation of bowel flora

Table 92 COMPLICATIONS OF CHEMOTHERAPY (*Continued*)

  4 *Staphylococcus aureus* enteritis
  5 Membranous colitis
  6 Stomatitis and pharyngitis due to *Candida*
  7 *Jaundice and hepatitis* (*sulfanilamide*)
  8 Liver damage (Aureomycin *intravenously in* quantities larger than 2 Gm per day)
  9 Proctitis
  10 Pruritus ani
  11 Steatorrhea
V Urinary tract complication
  1 Hematuria and crystalluria (sulfonamides)
  2 Lower nephron nephro is (sulfonamides)
  3 Obstruction to urine flow (sulfonami les)
  4 Albuminuria and cylindruria (streptomycin in a id urin)
  5 Nephrotoxicity with renal failure (bacitracin polymyxin and n omycin)
VI Nervous system complications
  1 *Injury* to peripheral nerves by direct injection of antibiotic solution
  2 Peripheral neuritis (broad-sp ctrum antibiotics)
  3 Paresthe ias (streptomycin polymyxin)
  4 Damage to eighth nerve (streptomycin dihydro-streptomycin neomycin)
  5 Encephalitis (some sulfonamides)
  6 Encephalopathy due to *excessive* intrathecal doses of penicillin or streptomycin
VII Complications in blood and blood forming organs
  1 Acute hemolytic anemia (sulfonamides)
  2 Eo inophilia
  3 Thrombopenia (streptomycin Chloromycetin)
  4 Granulopenia and aplastic anemia (rare Chloro-mycetin and streptomycin)
VIII Mi cellaneous complications
  1 Negative nitrogen balance (Aureomycin)
  2 Increased riboflavin excretion (Aureomycin)
  3 Electrolyte disturbances (streptomycin)
  4 Herxheimer reaction (penicillin in syphilis)
  5 Pulmonary embolism (accidental intravenous injection of solutions in oil or of insoluble salts of antibiotics)
  6 Thrombophlebitis (intravenous injection of Au reomycin)
  7 Changes in bacterial flora of body
IX Superinfections
  These occur with all chemotherapeutic agents. They are due to invasion by normally *present or* germs or by those acquired by contact with other patients or attendants or they may result from the accidental introduction *of bacteria* during injection of drug in all instances the new *infections are* produced by strains of organisms insensitive to the antibioti being administered at the time they first appear *Infections due to Candida* (*Monilia*) may also occur during chemotherapy they *may involve* the mouth pharynx or lung or they may become generalized when they may be fatal This *type of superinfection is* being reported more frequently and is particularly important because *no specific*

tal extraction This observation and the fact that transient bacteremia occurs in from 20 to 60 per cent of persons who have teeth removed have emphasized the importance of chemoprophylaxis in patients with acquired or congenital heart disease The sulfonamides have been used for this purpose but they are not the drug of choice Penicillin is the agent employed most often and it appears to be very effective in preventing infection of the cardiac valves although bacteremia may not always be eliminated

Patients with chronic bronchitis emphysema and bronchiectasis are highly susceptible to superimposed bacterial infections It has been reported that the administration of 0 5 Gm Chloromycetin daily to individuals with these disorders resulted in a reduction in respiratory infections of 50 per cent An attempt has also been made to reduce the number of infections in diabetes mellitus by giving Aureomycin daily Fewer respiratory and urinary tract infections have been observed in treated cases these observations require confirmation

Children with cystic fibrosis of the pancreas (mucoviscidosis) are particularly susceptible to infections of the lung especially by *S aureus* For this reason Aureomycin has been used as prophylaxis in this disease Although staphylococci can often be cultured from the respiratory tract of these patients while they are receiving this drug the risk of repeated episodes of pneumonia is sharply reduced and life is prolonged and made much more comfortable

Chemoprophylaxis of Surgical or Accidental Trauma One of the most common areas of use of chemoprophylactic agents has been in elective surgery The purpose of this has been to prevent postoperative pulmonary and other infections Although the general impression has been that the administration of antimicrobial agents results in a reduction in the incidence of postoperative infectious complications careful study has emphasized the failure of prophylaxis in such cases In a number of patients subjected to elective abdominal surgery and given antibiotic agents no significant difference in the frequency of postoperative sequelae has been found when compared to a group in which no chemotherapy was used An increase in the rate of infection of clean wounds after operation despite the prophylactic use of antibiotics due primarily to invasion by penicillin resistant *S aureus* has also been noted There is no evidence that the number of postoperative pulmonary complications is decreased by chemoprophylaxis

Antibiotics in various combinations have been used extensively for preparation of the bowel for surgery The agents employed most widely for this purpose have been the so called broad spectrum antibiotics sulfonamides and neomycin Although the number of organisms in the intestine may be markedly reduced complete sterilization has rarely if ever been accomplished While it may appear that the incidence of postoperative peritonitis has been decreased by this procedure adequate controlled investigations of this problem have not been carried out Furthermore the administration of large quantities or mixtures of antibiotics is not without danger pseudomembranous colitis or acute staphylococcal enteritis (either of which may be fatal) occasionally appears during the course of antibiotic preparation of the intestine for surgery

Surgical treatment of infected areas such as the tuberculous lung localized abscesses bronchiectasis and others is an indication for the use of chemoprophylaxis prior to and after operation In this type of surgery the administration of antimicrobial agents appears justified even in the face of the risks which may be involved The type of drug employed must be determined by the location and etiology of the infection In accidental wounds or burns chemoprophylaxis has not been so successful as might have been expected Infection is not completely prevented even when combinations of antibiotics are given in these instances the organisms involved are frequently *Proteus* or *Pseudomonas* The ineffectiveness of sulfonamide powder in preventing infection in wounds is well known

In obstetrical practice patients with prolonged and difficult labor are susceptible to puerperal infection and the use of an antibiotic to prevent this complication may be justified On the other hand the general application of chemoprophylaxis to all women after completion of labor is unjustified

Dangers of Chemoprophylaxis It is important to point out that the same untoward effects which occur when antibiotic agents are used for therapeutic purposes are observed when patients who have no active infection are given these drugs The risk of the development of reactions and the difficulties which they involve must always be taken into consideration in planning a program of chemoprophylaxis When there is no evidence that chemoprophylaxis will be effective it should not be given

COMPLICATIONS OF CHEMOTHERAPY

Complications resulting from the widespread use of various chemotherapeutic agents are steadily increasing in frequency All the available drugs produce one or another type of untoward effect Some of these effects are directly toxic some are allergic and others are related to the biologic activities of the chemotherapeutic substances The reasons for the increased incidence of undesirable sequelae to chemotherapy are mainly three (1) the increase in the number of antimicrobial agents each of which may produce such reactions (2) the increase in the

days is not likely to lead to the development of a serious situation or death The combination showing the greatest additive or synergistic effect should be used

For purposes of devising the most effective antibiotic combinations the drugs have been divided into groups (1) those which are primarily bactericidal—penicillin streptomycin bacitracin and neomycin and (2) those which are primarily bacteriostatic—Aureomycin Terramycin Achromycin Chloromycetin and erythromycin If there is insufficient time for an in vitro bacteriologic study to be carried out two antibiotics in the first group may be used in combination if each alone is partially effective against the causative organism If no two drugs in this group fit this criterion and a mixture of both bactericidal and bacteriostatic agents does this combination should be given in doses that will result in full therapeutic concentrations of each antibiotic at the site of the infection

MISUSES OF CHEMOTHERAPY

There is little doubt that these drugs are often used in many situations where they are not required and that even when they are indicated failure to utilize them properly may lead to a poor clinical result Listed below are the most common misuses of the chemotherapeutic agents

1 Treatment of obscure fever
2 Choice of ineffective antibiotic
3 Inadequate or excessive doses
4 Use in insusceptible infections—measles mumps varicella poliomyelitis rheumatic fever influenza herpes simplex herpes zoster viral influenza and undefined upper respiratory tract infections
5 Improper route of administration—failure to use drug locally in pleural or joint spaces
6 Continuation of therapy with a drug to which bacterial resistance has developed
7 Failure to stop treatment in presence of a serious toxic or allergic reaction
8 Failure to alter chemotherapy when superimposed infections with insensitive organisms occur
9 Prophylaxis of minor respiratory tract infections
10 Use of sulfonamides in prevention of wound infections
11 Use of improper combinations of chemotherapeutic agents
12 Reliance on chemotherapy or prophylaxis to the exclusion of necessary surgical intervention e g drainage of localized areas of infection

Probably the most frequent chemotherapeutic misuse arises from the treatment of fever of obscure origin The mere presence of fever in the absence of localizing signs does not necessarily indicate that the temperature elevation is due to an infectious disease (see p 72) In the absence of strong clinical evidence that a febrile episode is infectious in origin particularly when there is no detectable focus chemotherapy should be delayed until adequate clinical and laboratory studies have been carried out

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Table 92 COMPLICATIONS OF CHEMOTHERAPY (*Continued*)

agent for treatment of systemic involvement is presently available

Superinfections occur in about 2 per cent of patients who receive a chemotherapeutic agent The organs involved in the secondary infection are most frequently the same as those affected in the primary disease The organisms responsible for superinfections are often difficult to treat with the presently available antibacterial drugs The factors which predispose to the development of superinfection are (1) age of three years or less (2) primary disease of the lower respiratory tract (3) infection of the middle ear and (4) the use of a drug or combination of antibiotic agents which tend to have a broad antibacterial effect the wider the antimicrobial spectrum the greater is the danger of secondary bacterial invasion Superinfections appear most frequently on the fourth or fifth day after initiation of chemotherapy and may convert a benign self limited disease into a serious prolonged or even fatal one It is essential to carry out frequent bacteriologic studies whenever possible to determine changes in bacterial flora that may subsequently be responsible for a secondary infection The administration of an antibiotic active against the predominating organism and its elimination before it is responsible for infection may prevent the appearance of a complicating disease

X Development of a resistance by some bacteria to any of the chemotherapeutic drugs

None of the available antibacterial substances is free of the potentialities of producing trouble With some like the sulfonamides the risk of development of serious reactions is great with others like penicillin it is relatively small in comparison to the beneficial effects of the agent Two types of reaction are common to all the chemotherapeutic agents (1) the development of hypersensitivity and (2) the production of superinfections by resistant organisms

The fact that harmful effects may follow the use of these drugs should not discourage the physician from applying them in situations where they are definitely indicated It should however make him hesitant to employ them in cases where indications for their use are entirely absent or at most only slightly suggestive Moreover the appearance of reactions during the course of treatment does not always make the cessation of therapy mandatory especially if the drug used happens to be the only effective one available for the purpose required The severity and type of the reactions their expected course and the possibility of influencing them by proper management must all be weighed against the importance of the infection under treatment

COMBINATIONS OF CHEMOTHERAPEUTIC AGENTS

There is some evidence to suggest that the simultaneous administration of two or more antibacterial agents may be more effective in certain infections than the same drugs used individually in equal or larger amounts This evidence has been obtained largely from test tube experiments some of it has come from animal studies little from careful clinical investigation True synergistic effects are rarely derived from combinations of various chemotherapeutic substances Increased activity is usually additive With some combinations no change in antibacterial potency occurs With others one agent may to a varying degree inactivate the effectiveness of the other

There are a few chemotherapeutic combinations of proved value in clinical medicine In the management of cases of subacute bacterial endocarditis due to strains of *Streptococcus viridans* and enterococci which are relatively unresponsive to penicillin the addition of streptomycin may be helpful in effecting clinical cure In general brucellosis responds better to combinations of drugs than to single agents (see p 904) The infectious disease in which combined chemotherapy is most effective is tuberculosis The reasons for this have been pointed out above

In some of the meningitides due to organisms other than the tubercle bacillus combined chemotherapy is also more effective than single agents For example although streptomycin alone given intrathecally and intramuscularly is quite effective in the management of many cases of *H influenzae* meningitis the simultaneous use of sulfadiazine increases the number of recoveries and decreases the incidence of bacterial resistance

There is clinical support for the use of combined therapy in some infectious diseases In other situations however combinations of antibacterial substances are used because (1) satisfactory results are not obtained with a single drug (2) multiple organisms are present and (3) the causative agents have not or cannot be isolated In general the following practices appear to be sound

1 A single antibiotic can be used effectively in most infections caused by a single organism Occasionally a single antibiotic may be used in a mixed infection in which it has been proved to be of value for example penicillin in the therapy of lung abscess

2 In certain infections the proper combination of chemotherapeutic agents should be given from the start of therapy

3 If the infection does not fall into either of these categories the in vitro effect of combinations of various antibiotics should be studied provided the patient's illness is such that a delay of 2 or 3

used but has been largely abandoned because sulfonamides and antibiotics are effective against pneumococci of all types

Epidemiology Pneumococci are normal inhabitants of the upper respiratory tract in 5 to 60 per cent of the population depending upon the season Pneumococcal infection occurs predominantly during the winter months the ratio of infection in males and females is 3 2 and morbidity and mortality are higher for Negroes than whites Person to-person transmission by droplets is undoubtedly common but true epidemics of pneumococcal pneumonia are rare even in closed populations Patients with pneumococcal infection can be managed without isolation precautions

Pathogenesis The mechanism by which pneumococci damage tissue is obscure It is conceivable that toxic substances may be elaborated when they multiply in the body but no such toxin has been demonstrated It has been suggested that rapid growth of pneumococci interferes with essential metabolic processes in the host but this is supported by no firm evidence The capsular substance is known to be a necessary factor in virulence and it also protects the organism to a certain extent from engulfment by phagocytes

Invasion of the tissues of the nasopharynx rarely if ever occurs and "pneumococcal pharyngitis" is always a questionable diagnosis The organisms multiply readily and produce acute inflammation in the lung serous cavities and the endocardium The factors that ordinarily protect the lung from pneumococci include the mucus of the respiratory epithelium the direction and velocity of air currents and ciliary action Under circumstances which impair the effectiveness of these barriers pneumococci are carried to the alveoli in droplets of saliva or mucus and infection occurs pneumonia usually begins in the right lower right middle or left lower lobe Susceptibility to pneumococcal pneumonia seems to be related to common respiratory disease fatigue chilling and depression of the cough reflex Intoxication with alcohol is a well known predisposing factor and the infection is likely to be severe in alcoholics Patients with multiple myeloma are peculiarly susceptible to pneumococcal infection especially pneumonia and pneumococcal peritonitis is a frequent complication of the nephrotic syndrome in children In some parts of the world the pneumococcus is said to be a common cause of secondary infection in patients with brucellosis or trypanosomiasis Experimentally the production of pulmonary edema increases the susceptibility of animals to pneumococcal pneumonia and the frequency and severity of pneumonia in patients with chronic heart disease suggests that a similar situation also holds for man

In the pulmonary alveoli the organisms cause an outpouring of polymorphonuclear leukocytes and edema fluid The studies of Wood have shown that this fluid, which contains myriads of pneumococci spreads rapidly through bronchioles bronchi and the alveolar pores of Cohn As the infection develops neutrophils and macrophages begin to ingest pneumococci and the alveoli are filled with a fibrinous exudate containing many white cells but fewer and fewer organisms The peripheral zone of spreading edema can advance to involve additional lung tissue at a time when the older part of the lesion is actually undergoing resolution The outcome of the infection depends upon the rate at which bacteria in the edema fluid can multiply and spread into new areas as compared with the host s ability to immobilize and destroy them by phagocytosis

Bacteremia the result of entry into the blood by way of lymphatic vessels is common during the stage of spreading pulmonary infection indeed transient bacteremia probably occurs at the onset of nearly every pneumococcal infection in the lung Continued bacteremia is a poor prognostic sign not only because of the danger of metastatic infection but because it indicates poor localization of the pneumonic process

The resistance of the host to pneumococcal infection is greatly enhanced by specific antibody which not only enhances phagocytosis by "opsonizing" the organisms but as Rich has shown also retards the spread of bacteria in the tissues Recovery is not entirely dependent upon the immune response since antibody is not invariably demonstrable in patients who recover with or without chemotherapy However the dramatic recovery by crisis that used to occur before specific treatment became available usually coincided with the appearance of antibody in the blood With arrest of the infection the alveolar exudate undergoes liquefaction and the process resolves apparently by lymphatic removal of the inflammatory debris Pneumococcal pneumonia rarely produces necrosis of alveolar walls or bronchi and the lung is often restored to normal within a few days

In addition to producing pneumonia the pneumococcus can extend from the nasopharynx to produce otitis or mastoiditis paranasal sinusitis or meningitis from the lung it can extend to infect pleura pericardium or mediastinum and bacteremia may give rise to meningitis peritonitis arthritis endocarditis or other metastatic infections

PNEUMOCOCCAL PNEUMONIA

Pneumococcal pneumonia is a disease remarkable for its uniformity in contrast to other infections such as typhoid fever and tuberculosis The diseases

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Section 2 Infections Due to Gram-positive Cocci

111 PNEUMOCOCCAL INFECTIONS

Ivan L Bennett Jr

Etiology The pneumococcus is a gram positive encapsulated coccus that usually grows in pairs or short chains In the diplococcal form the adjacent margins are rounded and the opposite ends slightly pointed giving the organisms a lancet shape In stained preparations of exudate gram negative forms are often present Because pneumococci produce greenish discoloration of blood agar they are sometimes confused with alpha hemolytic streptococci The two organisms can be distinguished by the bile solubility and mouse virulence of the pneumococcus or by serologic typing A simpler method utilizing inhibition of pneumococci by Optochin impregnated paper disks is accurate and less cumbersome for routine use

The capsular substances are complex polysaccharides and are the basis for dividing pneumococci into serotypes Organisms exposed to type specific antiserum show capsular swelling the *Neufeld quellung reaction* by this means about seventy five serotypes have been identified All are pathogenic for man but types 1 2 3 5 7 and 8 are encountered most frequently in clinical practice Type 14 causes pneumonia in children but is rare in adults

Specific typing of pneumococci was of great clinical importance when therapeutic antiserum was

the gross appearance of infected fluid may not differ from that of a sterile pleural effusion later however there is profuse outpouring of polymorphonuclear leukocytes and fibrin resulting in an exudate of thick greenish pus containing large plaques of fibrin The quantity of exudate may become large enough to compress the lung and displace mediastinal structures In neglected cases this leads to extensive pleural scarring with limitation of chest movement Rupture and drainage through the chest wall (*empyema necessitatis*) can occur Metastatic *brain abscess* is an occasional complication of chronic pleural empyema the origin of this appears to be septic thrombi passing through the intercostal and vertebral veins

Pericarditis A particularly serious complication is spread of infection to the pericardial sac This may be manifested by pain in the precordial region and a friction rub synchronous with the heart beat although neither of these is always present The possibility of coexisting purulent pericarditis should be considered whenever there is pleural empyema especially when the patient appears gravely ill

Metastatic Infections *Arthritis* occurs more often in infants than in adults The affected joint is swollen red and painful with a purulent effusion It subsides promptly with systemic administration of penicillin

Acute bacterial endocarditis complicates pneumococcal pneumonia in less than 0 5 per cent of cases Its manifestations and treatment will be discussed later in this section

Meningitis another complication of pneumococcal pneumonia will also be discussed subsequently

Paralytic Ileus As already noted gaseous abdominal distention is commonly present In severely ill patients this may assume serious proportions such that the term *paralytic ileus* is justified The mechanism responsible for this disturbance cannot be exactly defined It may be related in part to acute infection plus hypoxia an additional factor may be poor diffusion of swallowed nitrogen because of the lowered oxygen content of arterial blood This complication further impairs respiratory movement and constitutes a difficult problem in management

Impaired Liver Function Alterations in liver function are very common during the course of pneumococcal pneumonia and jaundice is not at all rare The mechanism of the jaundice cannot be precisely defined

Laboratory Findings X *ray* of the chest reveals a homogeneous density in the affected area of lung In well-established cases the density may occupy one or more entire lobes whereas in early cases only a portion of one lung may be involved The white blood count usually shows a polymorphonuclear *leukocytosis* ranging from 12 000 to 25 000 per cubic millimeter Normal leukocyte count or leukopenia is sometimes observed in old people or in those with overwhelming infection and bacteremia The *blood culture* is positive for pneumococci during the first 3 or 4 days of illness in 20 to 25 per cent of cases The *sputum* when stained by Gram s method shows polymorphonuclear leukocytes and moderate numbers of gram positive cocci singly and in pairs These can be typed directly by the Neufeld capsular swelling technique but this procedure is not essential for present methods of therapy

DIFFERENTIAL DIAGNOSIS OF PNEUMONIA

Fever cough and pulmonary consolidation on physical or x ray examination form a symptom complex that can be produced by many diseases of infectious toxic or other etiology

Staphylococcal pneumonia (p 842) is likely to be encountered in children in adults during or after an epidemic of influenza and in debilitated elderly individual as a nosocomial infection The clinical picture is less uniform than that of pneumococcal pneumonia varying from bronchitis with few systemic symptoms to a fulminating infection Multiple chills hectic fever early formation of lung abscesses empyema and in infants pyopneumothorax suggest the diagnosis The sputum is often grossly bloody or purulent culture of sputum and blood establishes the diagnosis Positive blood cultures should alert the clinician to the possibility that pulmonary involvement is secondary to a focus of staphylococcal infection elsewhere in the body

Hemolytic streptococcal pneumonia (p 853) can also occur in association with influenza The clinical picture closely resembles that of pneumococcal pneumonia but multiple chills hectic fever early prostration and rapid pleural involvement with accumulation of fluid or associated streptococcal pharyngitis are often helpful signs Diagnosis can be made by blood and sputum culture or by finding a rise in antistreptolysin 0 titer in convalescent serum

Friedlander bacillus pneumonia (p 883) is commonest in males past middle age especially in alcoholics The patient is usually severely ill the sputum tends to be thick and tenacious physical findings in the chest are often surprisingly scanty despite massive consolidation by x ray nausea diarrhea jaundice and delirium are more frequent than in pneumococcal infections and large numbers of gram negative bacilli are usually present in stained smears of sputum

Tularemia (p 905) of the ulceroglandular or typhoidal type is often accompanied by pulmonary lesions There may be no respiratory symptoms and a paucity of physical signs or pleurisy hemoptysis

produced by different pneumococcal serotypes show little variation in severity or in clinical manifestations. The prognosis in type 3 pneumococcal pneumonia is usually regarded as poor; this is in large measure attributable to the frequency with which type 3 infections occur in patients with other debilitating diseases such as diabetes or congestive heart failure. However, the type 3 pneumococcus possesses an unusually thick capsule, is especially difficult for neutrophils to engulf, and is the pneumococcus most likely to produce abscess formation in the lungs of man and experimental animals; these facts suggest that its virulence is partly intrinsic and not wholly the result of its attacking susceptible hosts. It is still customary to classify pneumococcal pneumonias as *lobar*, a process involving one or more large segments or lobes of the lung, or *bronchopneumonia*, in which there is patchy involvement, usually of both lungs. This distinction now has little clinical importance; treatment is the same for both anatomic types when the etiologic organism is the same, and prognosis depends upon other factors. The usual lesion in adults is lobar in distribution, but in children and the aged bronchopneumonias are frequent.

Manifestations Pneumonia is frequently preceded for a few days by coryza or some other form of common respiratory disease. The onset is usually so abrupt that patients can often state the exact hour that illness began. There is a sudden *shaking chill* in more than 80 per cent of the cases, rapid rise in temperature, and corresponding tachycardia. It is unusual for patients with pneumococcal pneumonia to experience more than a single rigor unless antipyretic drugs are administered, and repeated chills should suggest another etiologic agent.

About 75 per cent of patients develop severe *pleuritic pain* and *cough* productive of pinkish or "rusty" mucoid sputum within a few hours. The chest pain is agonizing, and respirations become rapid, shallow, and grunting as the patient tries to splint the affected side. Many patients are mildly cyanotic and show dilatation of the alae nasae when first seen. Patients appear acutely ill, but nausea, headache, malaise, and other complaints are unusual, and most individuals are alert and far from prostrated; the pleuritic pain is the dominant complaint.

Physical examination reveals restricted motion of the affected hemithorax, impaired or flat percussion note with increased fremitus over the involved area, and, usually, decreased breath sounds. Later bronchial breathing, pectoriloquy, and fine moist rales are evident.

In the untreated disease there is sustained fever of 102.5 to 105 F, continued pleuritic pain, cough and sputum, and gaseous distention is frequent. Herpes labiales is a common complication. After 7 to 10 days there is diaphoresis, abrupt defervescence, and dramatic improvement in manifestations: the crisis.

In cases which terminate fatally there is usually extensive *pulmonary involvement, and dyspnea*, cyanosis, and tachycardia are prominent. Circulatory collapse or a picture resembling forward heart failure is common. Death in a few patients is associated with empyema or some other suppurative complication.

Effect of Specific Chemotherapy Pneumococcal pneumonia usually terminates promptly when an appropriate antimicrobial drug is given. Within 12 to 36 hr after initiation of treatment with penicillin, temperature, pulse, and respiration fall to normal, pleuritic pain subsides, and the spread of the inflammatory process is halted.

Complications The typical course of pneumococcal pneumonia just described can be modified by the development of one or more local or distant complications.

In the Lung *Atelectasis* of all or part of a lobe may occur during the active stage of pneumonia or after treatment has been instituted. The patient may complain of sudden recurrence of pleuritic pain and show rapid respirations. Small areas of atelectasis are sometimes detected by x-ray in the absence of symptoms. These areas usually clear with coughing and deep breathing, but bronchoscopic aspiration is occasionally necessary. If atelectasis is allowed to persist, the affected area becomes fibrotic and functionless. *Delayed resolution* The removal of exudate from the lung following pneumococcal infection is usually complete within a few days, but occasionally, especially in elderly individuals, consolidation persists for longer periods. Sometimes the involved area never becomes reaerated and fibrosis results. *Lung abscess* is a rare sequel to pneumococcal infection. It is manifested clinically by continued fever and profuse expectoration of purulent sputum. X-ray shows one or more cavities. This complication is exceedingly rare in patients who receive penicillin therapy and is more likely to result from type 3 infections.

In Adjacent Structures *Pleural effusion* is noted in about 5 per cent of patients with pneumococcal pneumonia, even with specific therapy. The amount of fluid is usually not sufficient to cause obvious displacement of mediastinal structures. If it does not become infected, it is spontaneously reabsorbed within a week or two.

Prior to the introduction of effective chemotherapy, pneumococcal infection of the pleura with *empyema* occurred in 5 to 8 per cent of patients with pneumococcal pneumonia; it is now observed in less than 1 per cent of treated cases. It is manifested by persistent fever or pleuritic pain, together with signs of pleural effusion. In the early stages

hilar nodes and foreign body are important causes of persistent collapse although plugging of bronchi by inspissated mucus is by far the most frequent cause

Pulmonary adenomatosis (p 1399) a diffuse neoplastic disease can be accompanied by fever profuse glairy sputum and hemoptysis with various x ray findings *and is sometimes mistaken at first* for acute bacterial pneumonia or tuberculosis

Pulmonary infarction is especially frequent in patients with congestive heart failure and after surgical procedures Prostatic surgery and parturition are particularly likely to lead to embolization from the pelvic veins Pulmonary embolization may be asymptomatic but in many patients there are sudden pleuritic pain dyspnea anxiety transient hypotension and hemoptysis Fever is common but true chills are rare Icterus may accompany pulmonary infarcts in individuals with congestive heart failure Signs of consolidation and pleural fluid are common and *often evidence of phlebo* thrombosis can be detected in the legs

Septic pulmonary infarcts with abscess formation and cavitation should always suggest puerperal sepsis or infected abortions with pelvic thrombophlebitis in a female For reasons that are obscure phlebothrombosis and pulmonary infarction are relatively frequent complications of convalescence from psittacosis

The lungs of patients with *uremia* sometimes show x ray changes consisting of infiltrations that flare toward the periphery from both hilar areas Roentgenographically the changes in the lungs of patients with *acute pulmonary edema* and *heart failure* are sometimes surprisingly well localized to a segment or lobe of one lung

The inhalation of *noxious materials or irritants* (p 1402) including smoke chlorine phosgene cadmium fumes bagasse fibers and other organic dusts can lead to bronchitis bronchiolitis and patchy or even lobar infiltration in the lung, dyspnea and low grade fever The diagnosis is usually made by eliciting a *history of exposure* The ingestion of gasoline or kerosene (p 775) is almost invariably complicated by severe chemical bronchopneumonia

Pneumonitis is detectable by physical examination or x ray in some patients with erythema multiforme (p 1710) lupus erythematosus (p 1700) rheumatic fever (p 861) or intestinal helminthiasis (pp 1120 and 1123) Infectious mononucleosis (p 1151) and lymphocytic choriomeningitis (p 1064) are sometimes accompanied by pulmonary infiltrations and occasionally by signs of respiratory irritation with cough and sputum Pulmonary lesions usually in the form of scattered nodular densities with accompanying cough dyspnea and cyanosis occur in a small proportion of patients with smallpox (p 1060) chickenpox (p 1058) or measles (p 1056) the involvement in these diseases is believed to be caused by the virus rather than by secondary bacterial invaders Rupture of amebic abscess into the pleural cavity can be mistaken for acute pneumonia (p 1110) and in a few patients with estivoautumnal malaria blockage of pulmonary capillaries by parasites can lead to confusion with respiratory infections of various types (p 1112)

PNEUMOCOCCAL MENINGITIS

The pneumococcus is second only to the meningococcus as a cause of purulent meningitis in adults in children influenzal meningitis is also more frequent than pneumococcal infection

Pneumococcal meningitis can develop as a "primary" disease without preceding signs of infection elsewhere as a complication of pneumococcal pneumonia by extension from otitis mastoiditis or sinusitis or following a skull fracture which creates an opening into the nasal cavity or paranasal sinuses Patients with pneumococcal endocarditis frequently develop meningeal infection Patients with multiple myeloma seem to be prone to pneumococcal infection of the meninges just as they are to pneumonia

The *manifestations* are those of any acute pyogenic meningitis and include chills fever headache nuchal rigidity Kernig and Brudzinski signs delirium and cranial nerve palsies Evidence of otitis sinusitis or pneumonia should be carefully sought by physical and roentgenographic examination in all patients

The *spinal fluid* is under increased pressure appears cloudy often with a greenish tint and shows a high protein and low glucose content Stained smears usually reveal myriads of gram positive diplococci and polymorphonuclear leukocytes in some patients the number of cells in the spinal fluid is surprisingly small much of the cloudiness being produced by the bacterial content

With appropriate chemotherapy recovery can be expected in 70 to 85 per cent of cases Before penicillin was available the mortality rate exceeded 95 per cent, and sulfonamides did little to reduce this Relapse can occur but is unusual if adequate treatment is carried out Subarachnoid block the result of accumulation of large amounts of thick exudate in the meningeal space and at the base of the brain is now an unusual complication.

PNEUMOCOCCAL ENDOCARDITIS

Endocarditis is almost always a complication of pneumonia The clinical picture is that of acute bacterial endocarditis (p 973) with remittent fever petechial hemorrhages splenomegaly and

and consolidation may dominate the clinical picture Patients are usually very ill with fevers of 104 to 106 F and the disease does not respond to penicillin Agglutinins for the organism may not appear until the third week A history of contact with wild rabbits or the finding of a cutaneous ulcer and regional lymphadenitis is helpful in diagnosis

Infection by other bacteria can produce pneumonia Pulmonary involvement is frequent in patients with *Salmonella* bacteremia especially in *Salmonella suipestifer* infections (p 890) *Hemophilus influenzae* is a common cause of lung disease in children in adults it occasionally produces a necrotizing bronchiolitis and in elderly patients with chronic lung disease it may produce bronchopneumonia (p 896) The diagnosis is usually made only by culture of sputum Pulmonary lesions with cough and hemoptysis can be prominent in Weil s disease (p 1014) and of course the plague bacillus can cause an overwhelming and rapidly fatal pneumonia especially when plague becomes epidemic (p 909) sporadic infection by *Pasteurella pestis* is more likely to be the bubonic form

Primary atypical pneumonia (p 1044) is usually more insidious in onset than bacterial pneumonias chills are infrequent fever is usually lower pleuritic pain and effusions are unusual headache and malaise are prominent the cough is hacking irritating and productive of small amounts of mucoid sputum rarely blood tinged and physical signs are scanty in comparison with x ray changes Herpes labialis is unusual The leukocyte count is usually normal although it may be increased during the second week of illness and in 30 to 50 per cent of cases cold agglutinins are demonstrable during the second week

Psittacosis (p 1052) is often described as a severe form of atypical pneumonia Actually most patients with this disease are febrile and have systemic symptoms of headache lethargy and malaise for several days before pulmonary lesions develop The pulse is usually slow in proportion to fever and patients are sometimes suspected of having typhoid A history of contact with parrots poultry or other birds may be helpful The leukocyte count is normal and diagnosis is established by finding complement fixing antibodies in rising titer Splenomegaly is present in a variable proportion of patients with psittacosis and is sometimes a clue to diagnosis

Q fever (p 1037) is characterized by severe headache sustained fever and usually minimal symptoms of respiratory disease although a large proportion of patients show roentgenographic evidence of patchy pulmonary involvement A history of contact with cattle suggests the possibility of Q fever which is widely distributed in this country

Acute tuberculous pneumonia (p 939) may be difficult to recognize because in the early stages tubercle bacilli may not be demonstrable in the sputum the early consolidation is often the result of an inflammatory response to discharge of tuberculin containing material into the lung Fever is usually remittent or intermittent and may not exceed 102 F Many patients with tuberculous pneumonia feel surprisingly well despite consolidation of an entire lobe *Pleurisy with effusion* is seldom abrupt in onset its course is prolonged and physical and x ray findings are those of accumulating pleural fluid rather than parenchymal consolidation The leukocyte count is usually normal Herpes labialis is rare in tuberculosis

Blastomycosis (p 987) can produce acute lobar or bronchopneumonia with high fever pleuritic pain dyspnea and pleural fluid The organisms are usually easily found in the sputum and cavitation develops early in the illness The usual course of pulmonary blastomycosis is less acute with low grade fever and slow evolution of the pulmonary findings Typical skin lesions of blastomycosis or concomitant involvement of bone are aids in diagnosis

Actinomycosis of the lung (p 984) is usually a more chronic disease than bacterial pneumonia and is more likely to be confused with tuberculosis or lung tumors The diagnosis is made by finding sulfur granules in sputum or by culturing the organism Other mycotic infections of the lung include *primary histoplasmosis* (p 991) which can produce an acute illness with fever cough and multiple nodular pulmonary densities that lasts for several weeks and *primary coccidioidomycosis* (p 988) distinguishable in endemic areas by pulmonary infiltration fever eosinophilia and often erythema nodosum

Lung abscess may have an abrupt onset with chill fever and pleuritic pain and can be confused with acute pneumonias The development of cavitation in a well circumscribed pulmonary density and profuse purulent sputum makes the diagnosis clear In individuals with chronic abscess weight loss is prominent and cavitation readily apparent There is usually intermittent or remittent fever A history of epilepsy alcoholic intoxication anesthesia dental extraction tonsillectomy or aspiration of a foreign body may be elicited Abscess may be the first sign of bronchogenic carcinoma

Atelectasis may occur in patients confined to bed especially if respiratory motion is limited (as after an abdominal operation) or when the cough reflex is depressed by drugs or central nervous system disease Infection of the collapsed pulmonary segment leads to fever pleuritic pain and purulent sputum There is often a shift of the mediastinum toward the affected side Tumor enlarged

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metastatic infection of the lungs meninges joints eye and other tissues The infection can attack normal valves and is particularly likely to occur on the aortic valve The valvular infection is destructive and loud murmurs and heart failure develop rapidly Rupture or perforation of cusps or even rupture of the aorta can occur The blood culture is consistently positive for the pneumococcus yet at the same time antibodies for the infecting organism can usually be demonstrated in the blood a combination of findings seldom observed except in endocarditis or brucellosis The rapid destruction of the valvular structures combined with a striking tendency to the development of myocardial abscess in the region of the valve ring makes pneumococcal endocarditis a difficult disease to cure despite the sensitivity of the organism to penicillin

PNEUMOCOCCAL PERITONITIS

Pneumococcal peritonitis occasionally occurs in young girls presumably the vagina and fallopian tubes are the portal of entry Symptoms are fever pain abdominal distention vomiting and accumulation of peritoneal fluid The diagnosis is made by examination of the purulent ascitic fluid blood cultures are often positive and a polymorphonuclear leukocytosis is the rule

Peritonitis is also a frequent complication of the nephrotic syndrome particularly in children in whom there may be repeated episodes of this infection

TREATMENT

Specific Chemotherapy Penicillin is the drug of choice in all pneumococcal infections The minimum curative dosage for *pneumonia* is less than 60 000 units daily and a total daily dose of 600 000 units as one injection of a depot preparation or multiple injections of aqueous crystalline penicillin provides a good margin of safety Treatment should be continued until the patient has been afebrile for 48 to 72 hr The response is usually dramatic and relapse is virtually unheard of Pneumococcal pneumonia can be treated adequately with oral penicillin in a dosage of 1 2 to 2 4 million units daily

Peritonitis usually responds within 36 to 48 hr to 600 000 units of penicillin daily

Pneumococcal *meningitis* is best treated with massive amounts of penicillin intramuscularly a minimum dosage is 12 million units of aqueous penicillin daily and in many clinics larger amounts are used and Benemid is also given to impede renal excretion of the antibiotic The intrathecal administration of penicillin in the amount of 5 000 or 10 000 units in 10 ml physiologic saline solution each day is still advocated by some but has been abandoned by most clinicians There is convincing evidence that the addition of sulfadiazine to this regimen affords no advantage and that the supplementary administration of chlortetracycline (and presumably other broad spectrum drugs) *actually* exerts a deleterious effect producing antibiotic antagonism (see p 830) In the presence of sinusitis or otitis surgical drainage should be carried out as soon as feasible The response of meningitis is usually less dramatic than that of pneumonia patients often remain febrile and disoriented and signs of meningeal irritation may persist for several days improvement becoming gradually evident with continued treatment

In *pneumococcal endocarditis* also large doses are required—6 to 12 million units daily by intramuscular injection Rapidly developing heart failure in these patients and the tendency to myocardial abscess formation however often lead to a fatal outcome despite large doses of antibiotics

Sulfonamides are effective in pneumococcal pneumonia but their action is not so prompt or dramatic as that of penicillin they are virtually useless in meningitis and endocarditis

The *tetracycline* drugs and *chloramphenicol* are effective in the treatment of pneumonia in doses of 1 0 to 2 0 Gm daily They are recommended only for patients who have exhibited an untoward reaction to penicillin

Arthritis responds to systemic penicillin aspiration and intraarticular instillation of the drug are rarely necessary *Empyema should be watched for* and treated as early as possible When an effusion is detected the fluid should be examined for organisms and if they are found 50 000 to 200 000 units of penicillin should be injected intrapleurally Daily aspiration of fluid and instillation of penicillin should be carried out until cultures are persistently negative Fluoroscopic guidance may be needed for aspiration of small empyema pockets If the exudate becomes especially thick and viscid streptokinase streptodornase (Varidase) may facilitate its withdrawal Aspiration of exudate and instillation of penicillin is treatment of choice in *pericarditis* also In empyema or pericarditis the development of loculation and thick exudate with difficulty in aspiration should lead to consideration of surgical drainage While there has been good success in the medical management of these infections of serous cavities thoracotomy will sometimes shorten a patient s hospital course and should not be neglected when difficulties develop in medical treatment

Other Measures *Oxygen* may be used for intense cyanosis in pneumonia but is likely to aggravate abdominal distention Codeine 30 to 60 mg every few hours will usually control mild *pleuritic pain* A chest binder or adhesive strapping of the affected

side may diminish pain but increases the likelihood of atelectasis and interferes with subsequent examinations When pain is severe intercostal nerve block by injection of 2 0 ml of 1 per cent procaine beneath the rib margins proximal to the site of pain is usually effective The procedure is not technically difficult or dangerous Other methods of relieving pleuritic pain are usually transient in their effect but are sometimes worth trying they include ethyl chloride spray over the painful area intravenous injection of calcium gluconate and intravenous injection of tetraethylammonium chloride

PROGNOSIS

With proper chemotherapy the mortality from pneumococcal pneumonia has fallen to less than 5 per cent and in many clinics to less than 1 per cent The recovery rate in meningitis is 70 to 85 per cent Pneumococcal endocarditis is still fatal in at least half the cases

Signs of poor prognosis in pneumonia include leukopenia circulatory collapse multilobar involvement and persistent bacteremia Jaundice is often prominent in fatal cases but icterus alone is not a poor prognostic finding

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112 STAPHYLOCOCCAL INFECTIONS

David E Rogers

Staphylococci cause the majority of superficial suppurative infections in man They are also responsible for certain infections of the lungs long bones and kidneys

In recent years staphylococcal infections have assumed increasing clinical importance because of their failure to respond satisfactorily to antimicrobial drugs Certain features of staphylococcal disease have helped to create this situation These are (1) the tendency of staphylococci to invade the tissues of debilitated patients (2) the rapid tissue destruction and abscess formation which characterize infection caused by these microorganisms and (3) the capacity of staphylococci to develop resistance to antibacterial drugs

BACTERIOLOGY

Staphylococci are members of the genus *Micrococcus* which includes many saprophytic cocci that do not cause human infection The parasitic micrococci of primary concern in medicine are now grouped in the species *Micrococcus pyogenes* Through established medical usage these pathogenic micrococci are termed *staphylococci* They are normal inhabitants of the skin and anterior nares of man

Staphylococci are spherical gram positive bacteria which grow abundantly in the usual meat extract or infusion media On solid media colonies develop characteristic pigmentation by which three varieties can be differentiated *Micrococcus pyogenes* var *aureus* (*Staphylococcus aureus*) grayish yellow *Micrococcus pyogenes* var *albus* (*Staphylococcus albus*) ivory white and *Micrococcus citreus* orange yellow Most human infections are caused by *S aureus* The name staphylococcus derives from the characteristic grapelike clusters of organisms seen in stained smears prepared from colonies growing on solid media (Greek *staphule*—grape) Examination of stained smears of pus shows

metastatic infection of the lungs meninges joints eye and other tissues The infection can attack normal valves and is particularly likely to occur on the aortic valve The valvular infection is destructive and loud murmurs and heart failure develop rapidly Rupture or perforation of cusps or even rupture of the aorta can occur The blood culture is consistently positive for the pneumococcus yet at the same time antibodies for the infecting organism can usually be demonstrated in the blood a combination of findings seldom observed except in endocarditis or brucellosis The rapid destruction of the valvular structures combined with a striking tendency to the development of myocardial abscess in the region of the valve ring makes pneumococcal endocarditis a difficult disease to cure despite the sensitivity of the organism to penicillin

PNEUMOCOCCAL PERITONITIS

Pneumococcal peritonitis occasionally occurs in young girls presumably the vagina and fallopian tubes are the portal of entry Symptoms are fever pain abdominal distention vomiting and accumulation of peritoneal fluid The diagnosis is made by examination of the purulent ascitic fluid blood cultures are often positive and a polymorphonuclear leukocytosis is the rule

Peritonitis is also a frequent complication of the nephrotic syndrome particularly in children in whom there may be repeated episodes of this infection

TREATMENT

Specific Chemotherapy Penicillin is the drug of choice in all pneumococcal infections The minimum curative dosage for *pneumonia* is less than 60 000 units daily and a total daily dose of 600 000 units as one injection of a depot preparation or multiple injections of aqueous crystalline penicillin provides a good margin of safety Treatment should be continued until the patient has been afebrile for 48 to 72 hr The response is usually dramatic and relapse is virtually unheard of Pneumococcal pneumonia can be treated adequately with oral penicillin in a dosage of 1 2 to 2 4 million units daily

Peritonitis usually responds within 36 to 48 hr to 600 000 units of penicillin daily

Pneumococcal *meningitis* is best treated with massive amounts of penicillin intramuscularly a minimum dosage is 12 million units of aqueous penicillin daily and in many clinics larger amounts are used and Benemid is also given to impede renal excretion of the antibiotic The intrathecal administration of penicillin in the amount of 5 000 or *10 000 units in 10 ml physiologic saline solution* each day is still advocated by some but has been abandoned by most clinicians There is convincing evidence that the addition of sulfadiazine to this regimen affords no advantage and that the supplementary administration of chlortetracycline (and presumably other broad spectrum drugs) actually exerts a deleterious effect producing antibiotic antagonism (see p 830) In the presence of sinusitis or otitis surgical drainage should be carried out as soon as feasible The response of meningitis is usually less dramatic than that of pneumonia patients often remain febrile and disoriented and signs of meningeal irritation may persist for several days improvement becoming gradually evident with continued treatment

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Other Measures *Oxygen* may be used for intense cyanosis in pneumonia but is likely to aggravate abdominal distention Codeine 30 to 60 mg every few hours will usually control mild *pleuritic pain* A chest binder or adhesive strapping of the affected

more frequent in infants than in adults Acute staphylococcal osteomyelitis is primarily a disease of children although this may be attributable solely to anatomic differences between growing and mature bones Abscess formation is less common and persistent bacteremia more frequent in infants than in adults

Nevertheless recurrent furunculosis is common at any age and conventional serologic techniques often fail to demonstrate humoral antibodies following prolonged staphylococcal infections Immunization of experimental animals with exotoxin coagulase or whole organisms will usually prolong the course of induced staphylococcal infections but does not prevent eventual death There is no firm evidence to indicate that staphylococcal infection in man can be significantly modified by vaccination or "desensitization using current techniques

Epidemiology Pathogenic staphylococci are normal residents of the anterior nares and skin of 30 to 60 per cent of human beings In certain groups notably hospital personnel and patients the carrier rate is consistently higher than in the general population Over 90 per cent of newborn infants in nurseries acquire staphylococci as a part of the flora of the nares by the age of 2 weeks

Staphylococci remain viable for long periods in dust and on blankets and clothing It is probable that organisms are frequently spread by the nasal discharges of carriers as airborne particles although active staphylococcal infections are believed by some to be a more likely source of cross infection than the simple carrier state

Antimicrobial Resistance The introduction of each drug effective against staphylococci has been followed by an increase in the number of strains specifically resistant to its action When penicillin first came into general use less than 10 per cent of staphylococci isolated from patients or carriers were resistant to penicillin in vitro By 1957 50 to 80 per cent of staphylococcal strains isolated from hospitalized patients throughout the world were insusceptible to penicillin Similar emergence of resistant staphylococci has followed the use of streptomycin the tetracyclines chloramphenicol and erythromycin The incidence of resistance to each different antibiotic correlates closely with the frequency of use of that particular drug

Most observations on the occurrence of strains resistant to antibiotics have been made in hospitals and similar institutions where antimicrobial usage is heaviest Many studies of nasal flora have shown that susceptible staphylococci carried by patients entering a hospital are likely to be replaced by drug resistant strains already present in the institutional environment these resistant strains are also acquired and carried by hospital personnel creating a permanent reservoir Staphylococci isolated from population groups outside hospitals have not shown such a striking increase in resistance This fact is of great importance in preliminary decisions regarding therapy of staphylococcal infections

SUPERFICIAL INFECTIONS

Simple infection of hair follicles manifested by a minute erythematous nodule without involvement of the surrounding skin or deeper tissues is termed *folliculitis* Chronic recurrent folliculitis of the beard area is called *sycosis barbae*

A more extensive infection of follicles or sebaceous glands which penetrates deeper tissues results in the familiar *furuncle* or *boil* Itching and mild pain in the area are soon followed by progressive local swelling and erythema The overlying skin becomes thinned tense shiny and exquisitely painful on pressure or motion Relief of pain is prompt after spontaneous or surgical drainage The acne of adolescence is often complicated by secondary furunculosis Staphylococcal infection of the apocrine sweat glands in the axillary and genital areas (*hidradenitis suppurativa*) can become deep seated and chronic prone to recurrence and scarring and extremely resistant to treatment other than total surgical excision

Staphylococcal infections in the thick fibrous inelastic skin of the neck and upper back frequently lead to the formation of a *carbuncle* The relative thickness and impermeability of the overlying skin leads to lateral extension and loculation of the suppurative process and a large indurated extremely painful lesion results Carbuncles are generally accompanied by rigors fever leukocytosis and prostration Bacteremia is common

OSTEOMYELITIS

Staphylococci are responsible for the majority of cases of *acute osteomyelitis* This infection occurs almost exclusively in children under the age of twelve and is slightly commoner in males Bone involvement follows the hematogenous dissemination of bacteria At least 50 per cent of patients give a history of a recent furuncle or other superficial staphylococcal infection The frequent localization of the disease in the diaphyseal end of long bones is thought to be a result of the endarterial circulation to the diaphysis Approximately 25 per cent of patients also give a history of trauma to the involved area

Once established the infection spreads through the growing juxtaepiphyseal bone to the periosteum or along the marrow cavity If the process reaches the subperiosteal space the periosteum is lifted a subperiosteal abscess forms and rupture with infection of the subcutaneous tissues can occur

the bacteria in small clusters diploids or short chains In such preparations staphylococci retain their uniform roundness in contrast to the elongated forms assumed by pneumococci Staphylococci can often be seen within the cytoplasm of polymorphonuclear leukocytes in pus an uncommon finding in other gram positive coccal infections

Several laboratory methods can be used to recognize pathogenic staphylococci Most strains isolated from active infections lyse rabbit human and sheep erythrocytes ferment mannite and hydrolyze phenolpthalein phosphate A majority of pathogenic strains produce coagulase a substance which reacts with a factor in serum to produce a thrombin like product that clots human plasma This serum cofactor is lacking in many lower animals Other toxic products of staphylococci are mentioned below

Different strains of pathogenic staphylococci can be recognized by specific patterns of lysis by bacteriophages Although techniques are cumbersome this is the only precise method of typing now available

PATHOGENESIS

Little is known of the events which allow staphylococci living symbiotically with the human host to become invasive and produce active disease Strains of staphylococci capable of producing infection are common skin inhabitants and more than 50 per cent of serious staphylococcal infections of deep tissue arise from skin lesions A lesser number originate in the respiratory or genitourinary tract

Certain situations are known to predispose to staphylococcal disease *Diabetic patients* have a higher incidence of staphylococcal infections Under circumstances of severe *debilitation* or *malnutrition* in a population staphylococcal infections increase in frequency Staphylococcal infections are common when skin continuity is broken Abrasions wounds burns and skin areas denuded by exfoliative dermatitis are easily infected The incidence of superficial staphylococcal infection is high in individuals who work with greasy skin irritants *Influenza* and *measles* appear to predispose to invasion of the lower respiratory tract by staphylococci Recent studies indicate that broad spectrum antimicrobial therapy by suppression of the normal intestinal microflora occasionally allows the implantation or overgrowth of resistant strains in the gastrointestinal tract with the production of active disease Staphylococci can apparently invade the unbroken human integument via hair follicles and sebaceous glands

At local sites of infection active microbial multiplication is accompanied by inflammation and tissue necrosis Polymorphonuclear cells rapidly enter the area and ingest large numbers of microorganisms Thrombosis of surrounding capillaries occurs fibrin is deposited about the periphery and later fibroblasts create a relatively avascular wall about the area The fully developed staphylococcal lesion consists of a central core of dead and dying leukocytes and bacteria which gradually liquefies to form characteristic thick creamy pus surrounded by a fibroblastic wall the pyogenic membrane

From such an inflammatory focus in the skin staphylococci are often able to enter the blood stream Common sites of metastatic seeding are the diaphyseal ends of the long bones in children the lungs kidneys endocardium liver spleen and brain

Certain biologic properties of staphylococci are thought to contribute to pathogenicity Many strains elaborate an *exotoxin* (alpha toxin) capable of causing dermal necrosis in animals Fever tachycardia cyanosis shock and death ensue when this material is administered to experimental animals by the intravenous route a strikingly similar picture is seen in certain fulminating cases of staphylococcal bacteremia in man

The high correlation between *coagulase* production and virulence suggests that this substance is important in the pathogenesis of staphylococcal infections Although coagulase has been said to protect staphylococci from leukocytes active phagocytosis of coagulase positive staphylococci is readily demonstrable in vitro and in vivo Abscess formation is said to be less common in animal species that lack a coagulable plasma and in infants who show low titers of the serum coagulase reacting factor but the thesis that coagulase is responsible for focal abscess formation has been weakened by the recent demonstration that mice which lack a coagulable plasma develop typical abscesses during staphylococcal infections Recent studies suggest that coagulase may protect pathogenic staphylococci from bacteriostatic substances present in normal serum

Many pathogenic strains of staphylococcus can destroy human or rabbit leukocytes in vitro this has been attributed to a *leukocidin* Some strains produce *hyaluronidase* Many staphylococci are capable of elaborating an *enterotoxin* which produces nausea vomiting and diarrhea in certain experimental animals and in man

It has been established that pathogenic staphylococci can survive and even multiply within human or rabbit leukocytes This finding suggests that these cells may be a means of transporting the organisms and spreading infection to distant tissues

Immunity Clinical observation suggests that some degree of resistance to infection develops with age and perhaps experience with the staphylococcus Primary staphylococcal pneumonia is far

from which invasion of the blood stream can occur

Staphylococcal bacteremia is not a specific entity and manifestations in the individual patient depend upon the original source of the organisms and the site and extent of metastatic infections

Rarely patients with bacteremia die within 12 to 24 hr with high fever tachycardia cyanosis and vascular collapse More commonly the course is slower with hectic fever and progressive involvement of many organs and tissues Abscesses can form in the lungs bones kidneys brain, myocardium liver spleen or any other tissue Pustular or petechial skin lesions are common

The heart valves are often infected producing an endocarditis of the "malignant" or "ulcerative" type in which rupture of valve leaflets and valve ring abscess are common (see p 975) Staphylococcal endocarditis can also run a subacute course that is clinically indistinguishable from that produced by *Streptococcus viridans*

Staphylococcal bacteremia is generally accompanied by a polymorphonuclear leukocytosis of 12 000 to 20 000 but this is not invariable and a normal leukocyte count should never contradict the clinical diagnosis Anemia develops rapidly during the course of the illness

Prognosis Persistent staphylococcal bacteremia is an extremely serious disease Prior to the development of antimicrobials over 80 per cent of individuals succumbed usually within 2 weeks of the onset of illness The sulfonamides did little to alter this fatality rate but the combination of effective antibiotics and appropriate surgical measures results in recovery of 50 to 60 per cent of patients at the present time

STAPHYLOCOCCAL FOOD POISONING

Certain strains of staphylococci produce an enterotoxin which is responsible for many outbreaks of acute gastroenteritis Foods are contaminated from superficial infections in food handlers or by nasal droplets containing pathogenic staphylococci Cream filled pastries custards and cottage cheese subjected to improper refrigeration for a period allowing bacterial multiplication are frequently the source of outbreaks of staphylococcal infection

Symptoms typically appear 1 to 6 hr after ingestion of enterotoxin Onset is abrupt with severe nausea vomiting cramping abdominal pain diarrhea and prostration Low grade fever can occur but most patients are afebrile The disease is brief and self limited and requires only rest replacement of fluid loss and sedation Rare fatalities have occurred in the aged

Diagnosis can be surmised from the short incubation period the epidemic nature of the disease the short duration of symptoms and the lack of fever Etiology can be proved only if specimens of ingested food can be shown to contain large numbers of enterotoxigenic staphylococci

Staphylococcal enteritis a true infection of the gut that sometimes complicates therapy with antibiotics is described on p 1475

MISCELLANEOUS INFECTIONS

Staphylococci may cause otitis sinusitis or mastoid infections Certain strains elaborate an erythrogenic toxin that results in a rash indistinguishable from streptococcal scarlet fever Pyelonephritis and lower urinary tract infections may be staphylococcal in origin Epidemics of staphylococcal pyoderma in newborn infants and maternal breast abscesses are a recurring problem in many clinical maternity units

THE CHANGING PATTERN OF STAPHYLOCOCCAL INFECTIONS

Changes have occurred in the relative incidence of certain staphylococcal infections In prolonging the life span of patients with serious illnesses a group of individuals with increased susceptibility to many infections has been developed The adrenal steroids corticotropins nitrogen mustards and the folic acid antagonists appear to alter host defense mechanisms New surgical procedures have created many new portals of entry for microorganisms In this setting staphylococcal infections (along with gram negative bacillary infections and certain fungous infections) have become an increasing problem

In debilitated hospitalized patients staphylococcal infections are commonly atypical appear to be contracted from hospital personnel and are generally caused by antimicrobial resistant strains of staphylococci

Staphylococcal pneumonia formerly rare now occurs as a terminal complication of many disease states Postoperative wound infections due to staphylococci have increased in frequency Staphylococcal bacteremia arising in the hospital is not uncommon and staphylococcal enteritis is almost exclusively a hospital disease

There is little to suggest that staphylococcal strains resistant to antimicrobials are *any more invasive* than those which have always been prevalent Nevertheless the disease *states in which* staphylococcal infections now commonly arise are often of themselves critical Staphylococcal infec*tions in these* situations continue to carry a high mortality

Rarely the joint capsule is penetrated early and the presenting picture is pyogenic arthritis There is rapid death of bone (sequestration) followed by the laying down of new bone (the involucrum) producing characteristic roentgenographic changes Occasionally indolent staphylococcal infections of bone remain localized within dense granulation tissue about a central necrotic cavity Such a local infection can persist for many years as a so called *Brodie s abscess*

Osteomyelitis in children usually begins abruptly with chills high fever and pain at the local site Muscle spasm about the affected bone is often striking the child may refuse to move the limb and the tissues overlying the bony lesion soon become edematous Roentgenograms are usually normal for the first week but rarefaction local periosteal elevation and new bone formation are generally detectable during the second week of illness

In any patient child or adult with staphylococcal bacteremia secondary infection of bone can occur This tendency of staphylococcal infection to localize in bone is an important consideration in assessing the status of a patient with generalized abscess formation

Diagnosis *Osteomyelitis should be suspected in* any child with fever limb pain and leukocytosis History of a preceding cutaneous infection localized tenderness and the finding of *S aureus* in blood cultures are confirmatory In the early stages osteomyelitis must be differentiated from acute rheumatic fever poliomyelitis scurvy and syphilitic periostitis

Prognosis Prior to the advent of antimicrobials the mortality was approximately 25 per cent Chronic osteomyelitis with recurrent activation and metastatic spread to other bones was common Today acute staphylococcal osteomyelitis is declining in incidence death is rare and chronic osteomyelitis is disappearing

STAPHYLOCOCCAL PNEUMONIA

Staphylococci are the cause of 1 to 5 per cent of bacterial pneumonias The disease is sporadic except for the transient increase in cases that regularly accompanies epidemics of influenza

Primary staphylococcal pneumonia in infants and young children is a frequent cause of pyopneumothorax This complication occurs early in the disease and its presence should immediately suggest *S aureus* as the etiologic agent of a pulmonary infection In older children and adults staphylococcal pneumonia is usually secondary to influenza measles or whooping cough During the past few years staphylococcal pneumonia has come to occur with increasing frequency as a nosocomial infection in hospitalized patients with leukemia mucoviscidosis diffuse collagen disease and other chronic debilitating disorders

Staphylococci generally produce patchy centrally located pulmonary lesions pleurisy empyema and residual parenchymal abscesses are common

Staphylococcal pneumonia usually begins abruptly with repeated chills high fever progressive dyspnea cyanosis cough and pleural pain As in any serious staphylococcal infection peripheral vascular collapse may appear early and examination frequently reveals a patient who seems sicker than the physical findings would suggest Sputum is not characteristic although it may become purulent resembling the contents of a furuncle

Pulmonary infection in the form of multiple abscesses or patchy pneumonia can arise as a result of seeding of the lung from staphylococcal infection elsewhere in the body In primary staphylococcal pneumonia bacteremia is demonstrable in only about 20 per cent of cases It is far more common to obtain positive blood cultures if the lung lesions are secondary to bacteremic spread from another site For this reason the finding of staphylococcemia in a patient with pneumonia should lead to a *vigorous search for a primary focus of infection* in another organ

Diagnosis The sputum contains masses of polymorphonuclear leukocytes and bacteria The finding of numerous intraleukocytic cocci in stained smears of sputum strongly suggests the diagnosis The blood leukocyte count usually exceeds 15 000 with a marked increase in immature granulocyte forms but an initial leukopenia can occur Blood cultures are positive in less than 20 per cent of cases

Suddenly developing pneumonia with high fever and leukocytosis in debilitated hospitalized patients receiving antimicrobials should be considered staphylococcal in origin

Prognosis Prior to 1942 mortality ranged from 50 to 95 per cent The presence of bacteremia was almost invariably associated with a fatal outcome Prognosis has improved with the use of antibiotics but from 15 to 50 per cent of patients fail to survive The tendency to abscess formation and the frequency of pleural infection prolong convalescence in many patients

STAPHYLOCOCCAL BACTEREMIA

Staphylococcal bacteremia can originate from any type of local staphylococcal lesion Trauma to local lesions pinching squeezing or even surgical drainage often precipitates transient bacteremia with subsequent spread of infection multiple abscess formation and the creation of additional sites

continued for a minimum of 4 weeks and should be extended to 6 weeks to 3 months in the management of staphylococcal endocarditis

Superficial Infections Any of the antistaphylococcal drugs may abort the full development of a furuncle if treatment is initiated before localization and central necrosis have occurred Once frank abscess formation has ensued antimicrobials do little to modify the local lesion although they may prevent secondary superficial lesions or blood stream metastasis Antimicrobial drugs should be continued for 10 to 14 days if administered and should be used in conjunction with local moist heat immobilization of the affected part and strict attention to soap and water cleanliness Local manipulation of the lesion should be avoided unless surgical drainage is required Moist heat should be discontinued when drainage occurs to prevent maceration of the surrounding skin and the development of secondary furuncles The surrounding skin should be protected with a heavy coating of zinc oxide during the drainage period The use of topical antimicrobial creams (tyrothricin neomycin bacitracin) about the furuncle has been suggested to prevent satellite seeding *Bouts of recurrent furunculosis are difficult* to control sometimes they can be aborted by the administration of penicillin or other antistaphylococcal agents in full doses for 2 to 3 weeks in conjunction with general hygienic measures

Empyema Empyema should be treated by aspiration and the instillation of 200 000 to 500 000 units of penicillin every 24 to 48 hr Streptomycin 200 to 1 000 mg may also be instilled If loculation and thick exudate prevent adequate needle drainage the local instillation of streptokinase and streptodornase may aid in liquefying the exudate The removal of exudate is the most important aspect of therapy and surgical drainage should be promptly performed if the above measures fail

Osteomyelitis Acute osteomyelitis generally responds promptly to antimicrobial therapy Aqueous *penicillin 300 000 to 1 000 000 units should* be given every 4 hours and continued for 14 to 28 days

If the illness is rapidly progressing or an antimicrobial resistant strain is suspected streptomycin or erythromycin should be administered along with penicillin Bacitracin may be of value in certain cases Local drainage of abscess cavities in the soft tissues or bone is sometimes required and should be promptly considered in all patients where response to antimicrobials is inadequate or delayed *Sequestration should be handled surgically*

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113 HEMOLYTIC STREPTOCOCCAL INFECTIONS (Including Rheumatic Fever and Glomerulonephritis)

Charles H Rammelkamp Jr

Advances in the knowledge of streptococcal infections in the past few decades have made it increasingly clear that aerobic streptococci as a group are probably among the most important bacterial pathogens for man These bacteria may invade any tissue or organ and depending on the site of invasion and the parasite host relationship produce different clinical syndromes *Streptococcal* infections may be divided conveniently into two large groups The acute and often dramatic illnesses such as sore throat scarlet fever erysipelas puerperal fever and lymphangitis are included in the first group These infections occur *frequently and are characterized by* certain toxic septic or suppurative features The second group of diseases have been called the late nonsuppurative complications of streptococcal infections These illnesses which include acute rheumatic fever and acute glomerulonephritis commonly become manifest 2

TREATMENT

Features of Staphylococcal Infections Which Influence Therapy Certain features of staphylococcal infections bear emphasis in considering therapy

1 Staphylococci produce rapid necrosis and destruction of tissues Delays in effective therapy may convert an acute reversible illness into a chronic suppurative disease which responds slowly if at all to antimicrobial therapy

2 Frank abscess formation is common Antimicrobials of any type are almost completely ineffective in the presence of extensive necrosis or suppuration Successful cure frequently depends on prompt surgical drainage of all accessible suppurative foci

3 Staphylococci are killed slowly by antimicrobials under even optimal circumstances Infections tend to become chronic and relapses are frequent when therapy is withdrawn Thus antimicrobial therapy should be continued longer than in many bacterial infections

4 The changing patterns of staphylococcal antibiotic susceptibility have made in vitro sensitivity tests of great importance in the choice of appropriate antibiotic agents No single antimicrobial regimen has been found universally effective

Initial Treatment of Systemic Infections When serious staphylococcal infections are suspected appropriate cultures should be obtained and treatment started immediately with aqueous penicillin 500 000 to 2 000 000 units intramuscularly every 2 hr Surgical drainage of local foci should be carried out promptly When staphylococcal infection has arisen within the hospital or in other situations in which antimicrobial resistant strains are common a companion antimicrobial agent should be administered concurrently The choice of a companion drug will depend in part on the nature of the antimicrobial resistant strains prevalent within a given community Erythromycin and chloramphenicol 2 to 4 Gm daily in divided doses by the oral route are currently the companion drugs most frequently used at the New York Hospital because of the high incidence of strains sensitive to these agents in vitro In many hospitals erythromycin is reserved primarily for use in serious staphylococcal infections to reduce the hospital spread of erythromycin resistant strains and thus preserve its effectiveness

Changes in Therapy Established staphylococcal infections respond slowly to even the most effective antimicrobial regimens making it difficult to know when therapy should be considered inadequate Characteristically 24 to 48 hr elapse before a decline in fever is noted and recovery is accompanied by slow return of the temperature to normal in 7 to 10 days If the disease process shows evidence of rapid progression during the first 24 to 48 hr of treatment or if fever remains high for over 96 hr in the absence of detectable abscess formation antimicrobial therapy should be revised

While in vitro sensitivity studies are of great value the clinical response of the patient is the most important index on which to base changes in antimicrobial therapy If the response to initial therapy is satisfactory it should be continued regardless of in vitro evidence of resistance of the staphylococcus isolated If changes in therapy are indicated by the clinical course other antimicrobials should be selected on the basis of their in vitro activity against the strain under treatment.

Other antimicrobial drugs which have been found of value in the management of staphylococcal infections include the tetracyclines streptomycin novobiocin and bacitracin All these agents plus erythromycin and chloramphenicol have been used successfully alone or in various other combinations in the treatment of certain staphylococcal infections

Erythromycin and chloramphenicol administered together are currently used as the primary treatment of serious staphylococcal disease in some hospitals Streptomycin or dihydrostreptomycin 2 Gm daily has been a useful antistaphylococcal agent when used in conjunction with large amounts of aqueous penicillin The tetracyclines in 2 to 4 Gm daily doses are effective in the treatment of infections due to susceptible strains

Most strains of staphylococci now isolated (1957) are sensitive to novobiocin and this drug has been valuable when used alone or together with other antibiotics in selected staphylococcal infections Certain serious antimicrobial resistant staphylococcal infections have responded to bacitracin alone 15 000 to 25 000 units given every 6 hr or to bacitracin in combination with penicillin or streptomycin Bacitracin should not be used where renal impairment is evident and should be halted if evidence of declining renal function follows its use

The use of two or more antimicrobial agents concurrently has arisen from two considerations (1) the large number of therapeutic failures with any single antibiotic has led to the use of multiple drugs because of an unwillingness to withhold any agent of possible benefit to the patient (2) there is in vitro evidence that the emergence of resistant strains can be delayed by the simultaneous use of two or more antibiotics

It should be noted that to date there is no convincing proof that combined antibiotic therapy is superior in treatment of staphylococcal infections and that increasing resistance of strains in deep seated staphylococcal infections under treatment is actually rare

The therapeutic regimens outlined above apply to the management of staphylococcal pneumonia bacteremia and endocarditis Treatment should be

The exact role of streptokinase in the infectious process is not known The spreading nature of streptococcal infections has been thought to be due to streptokinase which breaks down the fibrin barrier

Following infection in man by a strain of group A streptococcus which produces large amounts of streptokinase antibody usually develops which specifically prevents the lysis of fibrin Thus the measurement of antistreptokinase may aid in diagnosis This serologic test is not so useful a diagnostic tool as the antistreptolysin test because not all group A streptococci produce sufficient streptokinase to stimulate antibody formation

Streptodornase (desoxyribonuclease) is an enzyme produced by several groups of streptococci This enzyme depolymerizes desoxyribonucleoprotein and desoxyribonucleic acid the two substances which account for the high viscosity of exudates A preparation of streptokinase streptodornase (SK SD) is now available for injection into body cavities containing pus or blood Such therapy results in the liquefaction of the fibrin and cellular debris

Other substances produced by streptococci are leukocidin hyaluronidase and streptococcal proteinase Leukocidin which is probably identical with streptolysin O is able to inhibit phagocytosis in vitro The enzyme hyaluronidase or spreading factor undoubtedly facilitates the spread of bacteria by increasing tissue permeability It is produced in large quantities by types 4 and 22 of group A streptococci

ACUTE STREPTOCOCCAL INFECTIONS

Epidemiology

Aerobic streptococcal infections are observed in all races in both sexes and at all ages Furthermore they occur during any season of the year throughout the world The *incidence* and the *clinical manifestations are altered by certain of the above factors* Thus streptococcal respiratory infections including scarlet fever are encountered especially during the colder months of the year Scarlet fever is rare in the tropics Under the age of three months streptococcal infections are rare and when they occur are associated with a high mortality Between the ages of six months and ten years scarlet fever is prominent Tonsillitis and pharyngitis are especially prevalent throughout childhood and early adult life In the female during the child bearing period puerperal infections caused by streptococci are occasionally observed Finally erysipelas which may occur at any age appears to be more prevalent in infants and the older age groups

Soon after birth alpha streptococci appear in the upper respiratory tract and may be isolated there from throughout life Streptococci of Lancefield groups C and G and more rarely organisms of groups other than A may be isolated from the oropharynx of 5 per cent or more of the normal population Occasionally group C and G streptococci cause tonsillitis

The group A flora of the oropharynx of any population group is made up of many different specific types but usually several types predominate In general at least 5 per cent of the people of any community harbor group A streptococci The prevalence varies and depends upon the cultural methods used as well as upon environmental host and bacterial factors Persons under twenty years of age especially if the tonsils are present are most likely to harbor group A streptococci

Studies of carriers of group A streptococci suggest that many are convalescent carriers that is they recently suffered either an apparent or an unapparent infection This appears to be especially *likely if large numbers of streptococci are isolated* from the oropharynx Such individuals frequently give a history of a recent illness and the antistreptolysin titer of their serum is high These data suggest that streptococci of group A rarely occur in the throat in large numbers except immediately before during or after an infection Once an individual has been infected he may remain a carrier for many months As the carrier state progresses the streptococci lose their ability to produce M protein

Ability to spread disease appears to be an attribute of individuals who have recently been infected Whether this is because such persons harbor numerous streptococci in the nose and throat or because the organisms are especially capable of parasitizing another person cannot be determined from the available evidence It is established that nasal carriers of group A streptococci are especially likely to spread disease

Respiratory pathogens are believed to be spread by two mechanisms (1) *directly* between two persons by *physical contact or by droplets passing* through the air for short distances (2) *indirectly* by droplet nuclei dust and fomites Recent studies have shown however that group A streptococci naturally deposited in dust and on blankets will not produce respiratory infections in man The evidence implicates the direct mode of transfer as primarily responsible for dissemination of such infections

The spread of streptococci in any population group must also be related to the degree of exposure Thus during the winter months when people are confined to enclosed areas and under crowded conditions dissemination of bacteria is especially likely to occur

Outbreaks of streptococcal infection occasionally *occur following the contamination of food* Such

to 3 weeks after an acute streptococcal infection These diseases assume major importance because they may be followed by chronic valvular heart disease or possibly by chronic nephritis

History Although scarlet fever was recognized in 1676 by Sydenham rheumatic fever and acute nephritis were not well described until 1805 and 1836 respectively The role of the streptococcus as the inciting agent of scarlet fever was established in 1924 With the realization that rheumatic fever and nephritis were related to streptococcal infections methods for the control and management of these nonsuppurative complications developed rapidly

Bacteriology Streptococci are gram positive and tend to form chains When streptococci are grown on a sheep blood agar plate it is possible to divide them into three groups *Alpha* colonies show a zone of incomplete or green hemolysis *beta* streptococci exhibit a clear zone of complete hemolysis and finally *gamma* streptococci produce no visible change in the blood agar Such a simple procedure as streaking a culture on a blood agar plate is sufficient to indicate the important pathogenic streptococci because those exhibiting *beta* hemolysis are responsible for the majority of infections in man

On the basis of a specific carbohydrate 12 groups of streptococci have been identified and designated A B C D E F G H K L M and N Respiratory infections are caused by group A and only rarely by groups C and G streptococci Group D streptococcus previously referred to as *Streptococcus faecalis* or enterococci inhabits the gastrointestinal tract and is responsible for infections of the abdominal cavity and the urinary tract

Not only may streptococci be classified by grouping but also most groups contain several different types Group A of primary interest to the clinician comprises at least 40 specific types Typing is based either on an agglutinin reaction or on the precipitin test The type specific antigen is the T substance in the former method the M substance in the latter

By grouping and typing streptococci considerable information has been accumulated concerning streptococcal infections from both a theoretic and a practical standpoint The carbohydrate responsible for the group characteristics is nontoxic and unassociated with virulence or immunity In contrast the M protein which tags the organism as the polysaccharide tags the pneumococcus is identified by typing is antigenic and is probably responsible in part for the virulence of the organism as well as for type specific immunity Glossy forms of group A streptococci which contain no M substance are avirulent whereas virulent organisms always contain this specific protein The T substance is not related to virulence

Several substances produced during the growth of beta streptococci serve to differentiate these organisms from other streptococci as well as to explain in part their pathogenic effects The type of hemolysis has been used as described above for classification of these bacteria Of the various hemolysins produced by streptococci at least two types have been recognized and termed *streptolysin O* and *streptolysin S* They are produced by streptococci of Lancefield groups A C and G the three organisms which cause the majority of human infections The role of these hemolysins in infections in man is not definitely known but they may be responsible for the anemia observed during the course of certain streptococcal diseases In man infections due to streptococci of groups A C and G result in the production of antistreptolysin O Approximately 85 per cent of patients develop antistreptolysin O during the second to third week of convalescence It is apparent then that the determination of the antistreptolysin titers of acute and convalescent serums may establish the diagnosis since an increase in titer occurs following a streptococcal infection

Another filtrable toxin produced by group A streptococci is the erythrogenic or *scarlatinal toxin* It is so named because it causes a scarlatiniform rash when injected into man and if sufficient quantities are given there may be fever and nausea That this toxin is responsible for the rash and toxic features of scarlet fever is well established Trask and Blake were able to demonstrate a toxin in the circulating blood of patients with scarlet fever and showed that it was neutralized by specific antitoxin Using the erythrogenic toxin as an antigen a skin test for susceptibility to scarlet fever was developed by the Dicks When one skin test dose is injected intradermally persons susceptible to the erythrogenic toxin respond with an area of erythema which reaches its maximum within 24 hr Persons exhibiting this skin reaction are susceptible to scarlatiniform rashes when infected by streptococci which produce erythrogenic toxin It should be emphasized that individuals exhibiting a negative Dick skin test although generally immune to scarlet fever are not immune to infection by group A streptococci The occasional occurrence of second attacks of scarlet fever may be explained by the fact that there are at least two types of immunologically distinct erythrogenic toxins

In 1933 it was observed that hemolytic streptococci rapidly liquefied human fibrin The extracellular substance responsible for this action is termed *streptokinase* Streptokinase does not lyse the fibrin directly but activates a serum enzyme plasminogen which in turn lyses the clot Streptokinase is produced by strains of Lancefield groups A C and G and only occasionally in small amounts by groups B and F

Pathogenesis

Streptococci gain entrance to the body primarily through the upper respiratory tract The organisms lodging on the mucous membranes or on other tissues probably remain viable for relatively short periods unless they actually invade the tissues In the nose and throat there is ample opportunity for invasion The organisms usually gain entrance through the lymphoid tissues of the throat especially the tonsils whose crypts apparently offer an ideal locus Occasionally the primary infection may be in the paranasal sinuses

The factors which determine whether an infection follows exposure to the organism are multiple The *dosage* or number of streptococci is apparently a decisive factor Infection usually results when there is exposure to large numbers of group A streptococci as occurs in food borne outbreaks Under natural conditions of spread the number of organisms acquired is dependent in part on the duration and intimacy of exposure to the organism

The second factor in relation to the organism is *virulence* In general little is known concerning this important feature Streptococci of groups other than A may be considered relatively avirulent when implanted in the lymphoid tissues of the throat The virulence of the group A organism may be related to their M antigenic component Whether there is variation in the virulence of the group A streptococci according to the specific type is not definitely known nor is there much evidence that rapid passage of a given type from man to man increases the virulence of the organisms although this is a common belief

Perhaps as important as the organism itself is the susceptibility of the host It is stated that a recent or simultaneous infection with one of the common respiratory viruses renders the host more susceptible to bacterial invasion Experience during the First World War would seem to indicate that influenza does indeed make one more susceptible to bacterial infections Whether the common cold or acute respiratory disease acts in a similar fashion is not known

Whether the group A streptococcus gains a foothold in the tissues is also governed by the immune status of the host The presence of type specific antibodies undoubtedly protects the individual against invasion by the streptococcus

When the bacteria begin to multiply in the infected tissues they produce certain toxic substances which account for the clinical manifestations of disease For example some of the constitutional symptoms observed in patients with scarlet fever are believed to be due to the erythrogenic toxin Usually the mucous membrane is denuded and covered by a thin yellow white or gray exudate Edema and hyperemia of the lymphoid tissues are present The lymphatics are dilated The regional cervical lymph nodes are enlarged

The organisms may invade the blood stream if the local defense mechanism is not functioning adequately and cause either metastatic infections such as meningitis brain abscess and endocarditis or a generalized infection which without treatment almost invariably results in death Mallory and Keefer have studied the cellular changes in such patients as well as the disease process in patients dying during the acute phase of streptococcal infections without bacteremia In fulminating streptococcal infections the streptococci may be seen in blood vessels throughout the body as well as in the endothelial cells of the endocardium and in the perivascular areas There is little cellular reaction around the organisms but their distribution is similar to the distribution of those lesions observed in patients dying several days after onset of the infection In the latter cases foci of lymphocytes plasma cells and histiocytes are commonly found in the heart especially just under the surface endothelium and endocardium Such collections occur also in the perivascular connective tissues myocardium and pericardium Occasionally some of the foci show polymorphonuclear leukocytes In the kidneys interstitial nephritis is observed with focal areas of round cell infiltration in the tissue surrounding the tubules glomeruli and blood vessels Similar lesions may be observed in other organs including the lung portal areas of the liver and pancreas

Most streptococcal infections are of short duration the acute phase ending within 5 to 7 days The exact mechanism for recovery at this time has not been defined but as in other bacterial infections it is assumed that antibodies develop which aid in the destruction of the organism Perhaps the most important of these are the antibacterial substances Techniques for measuring these antibodies are difficult but it is apparent that following infection there is an increase in the bactericidal power of whole blood Such bactericidal action is type specific the patient is protected only against the infecting type of group A streptococci and not against other types of this group of organisms The duration of such antibacterial immunity is not known but recent studies have demonstrated antibodies for 5 to 10 years

Clinical Manifestations

Acute Tonsillitis Pharyngitis and Scarlet Fever

The terminology used to classify *streptococcal* infections of the upper respiratory tract has been in use for many years and was introduced *prior to* the time that it was realized that *scarlet fever* sep

outbreaks are dramatic in that a large number of persons are affected almost simultaneously Formerly this type of infection was termed *septic sore throat* aside from the fact that the infection is caused by a single type of streptococcus it varies clinically in no way from other streptococcal epidemics

Clinical studies have demonstrated that reinfection may occur by a second type of group A streptococcus in a patient recovering from streptococcal pharyngitis and tonsillitis

Primary infection of the upper respiratory tract is undoubtedly the most common form of streptococcal infection in man It is doubtful whether any one in the United States escapes one or more of these infections The disease occurs especially in individuals between the ages of one and twenty years but it may develop at any age It is especially prevalent in the Temperate Zones during the winter and early spring seasons In most areas the disease is endemic Epidemics are usually due to one or at the most several types of group A streptococci whereas many different types are responsible for cases of pharyngitis and tonsillitis occurring sporadically

Tonsillitis and *pharyngitis* due to the beta streptococcus are characterized by an acute sore throat which may or may not be accompanied by a cutaneous rash If a rash is observed a diagnosis of *scarlet fever* is made The occurrence of a rash is related to antitoxic immunity which may be measured by the Dick test

Studies of the Dick reaction in various population groups have shown that at birth and up to three months of age the test is usually negative By the age of one to two years 85 per cent of the reactions are positive There is a rapid decline in the positive reactors to a level of approximately 15 per cent at the age of ten During the rest of life the decline is gradual These results would indicate that children under the age of ten are most susceptible to scarlet fever and this is the age period when most scarlet fever occurs Following an attack of scarlet fever the Dick reaction usually becomes negative

The incidence of scarlet fever has not changed significantly in the past 30 years but there has been a spectacular decline in mortality Top reports a fatality rate in Detroit of 2 7 in 1920 1 3 in 1930 and 0 3 in 1940 The reason for the apparent decreasing severity of scarlet fever is not entirely clear

Infections of the *paranasal sinuses* and middle ear often develop following infection of the tonsils or pharynx Not only may they occur as a complication of streptococcal sore throat but they are also commonly seen following measles influenza pertussis and other respiratory infections

Bacterial pneumonia caused by aerobic streptococci accounts for less than 5 per cent of all cases of pneumonia The disease is almost invariably caused by group A streptococci and may arise secondarily to an infection of the upper respiratory tract Epidemics have been observed following influenza and measles It also is likely to occur in those individuals with chronic lung disease including asthma and bronchiectasis Streptococcal empyema a complication of pneumonia in most instances is observed most frequently in patients under thirty years of age

Formerly it was thought that *erysipelas* was caused by a specific strain of beta hemolytic streptococcus but it is now known that group A C or G streptococci may be isolated from the skin lesions Group A organisms are responsible for the majority of infections and the organisms may belong to any of the various types in this group Although there are examples of several people having contracted erysipelas following contact with a case in most instances it has been impossible to trace the infection to such contact Erysipelas tends to occur in the older age groups especially in those individuals with chronic disabling diseases Immunity does not develop in fact individuals who have suffered from one attack are more susceptible than the normal population In some of the recurrences however the organisms cannot be isolated from the skin lesions but may be found in the oropharynx It is suggested that in such instances the disease is due to absorption of some toxic product of the streptococcus which in turn causes the local inflammatory lesion in the skin that is altered in its reactivity

Wounds may be infected by contamination at the time of dressing by droplets from either the patient or the attending physician Another possible source of infection is dust *Lymphangitis* may arise from a minute abrasion

Numerous studies have indicated that either aerobic or anaerobic streptococci cause *puerperal sepsis* Approximately 70 per cent of fatal cases are due to beta hemolytic streptococci Most of the infections are caused by group A although an occasional case is due to streptococci belonging to group B C D or G Since the group A streptococcus is rarely isolated from the genital tract either before or after labor it is assumed that infection is extrinsic Careful study of the patient and all persons coming in contact with her has shown that similar types of group A streptococci can be isolated from 75 per cent of cultures obtained from the oropharynx of such a patient or those attending her It appears from these studies that infection is usually contracted from an outside source and occasionally from the respiratory tract of the patient herself

Course of Illness (Fig 137) The majority of upper respiratory illnesses caused by group A streptococci are self limited In adults the temperature usually returns to normal by the third to fourth day whereas in children fever may persist for 5 to 9 days The temperature curve is not characteristic, although there is usually a slight morning remission In patients with scarlet fever the temperature remains elevated until the rash has reached its maximum intensity Fever may last for several weeks but in such instances it is well to search for some suppurative complications The constitutional symptoms as well as the localizing symptom of sore throat usually disappear shortly after the fever subsides

The edema redness and exudate disappear rapidly and except for a few small isolated spots of exudate and a slight degree of redness the throat appears essentially normal shortly after the fever subsides The lymphoid tissues of the posterior pharynx as well as the tonsils decrease in size and by the third to sixth week appear to be normal The lymph nodes may not return to normal size for 6 weeks

When rash does occur it usually makes its appearance on the second day reaches its maximum intensity shortly thereafter and then begins to fade The exfoliation of the epithelium begins during the decline of the eruption and is seen first in those areas where the rash originally appeared By the sixth to seventh day it is more or less generalized On the hands and feet the skin sheds in flakes or more rarely an entire cast of the hand or foot may be observed The skin in these areas becomes dry hard and wrinkled The most typical form of desquamation is seen beneath the free edge of the fingernails A fissure appears under the edge of the nail and then widens revealing the soft pinkish underlying skin

Before the introduction of specific chemotherapeutic agents the mortality rate was in the neighborhood of 3 per cent it is now less than 0 5 per cent This may be because of treatment or because few severe forms of scarlet fever are seen today Streptococcal infections are likely to be fatal in the extremes of life and in those individuals with severe suppurative complications

Laboratory Findings In 80 per cent of patients the total leukocyte count is increased During the first 2 days of disease the average count is 14 000 and as the illness progresses it returns to normal values If the number of leukocytes remains elevated after 1 week evidence of a complication may be found During the first 2 days of illness eosinophils are rarely seen but convalescence is characterized by an increase of these cells Patients with scarlet fever are especially likely to exhibit an elevation of eosinophils Not infrequently a trace

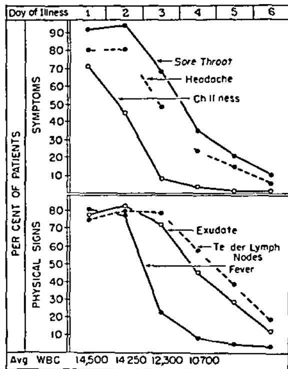


Fig 137 The natural course of group A streptococcal tonsillitis

of albumin may be found in the urine during the acute phase of the illness Rarely such specimens show a few red cells or casts Proteinuria occurring during the first 5 days of illness is transient and is not attended by serious sequelae

Cultures made on blood agar plates from a swab rubbed over the tonsils and oropharynx usually show a predominant growth of beta hemolytic streptococci Occasionally only a few colonies are observed Rarely no streptococci are isolated In the latter instance repeated cultures should be obtained The convalescent carrier state may continue for several months

Diagnosis Important features in the diagnosis of streptococcal pharyngitis and tonsillitis are the history of an acute onset of soreness on swallowing associated with feverishness and other constitutional symptoms The physical signs of diffuse redness and edema of the mucous membranes of the oropharynx tonsils and soft palate the presence of discrete to confluent exudate and enlargement and tenderness of the lymph nodes at the angle of the jaw are especially helpful These findings together with a leukocyte count of at least 12 000 suggest a streptococcal infection If the culture of the local lesion shows a predominant growth of beta streptococci the diagnosis is almost certainly established When only a few colonies grow on the blood agar

tic sore throat acute tonsillitis and *pharyngitis* with or without exudate were all caused by any of the numerous types of group A streptococci In these diseases the organism establishes itself in the lymphoid tissue *streptococcal lymphoiditis* might well be substituted for the above names As far as is known the course of the illness complications and sequelae are similar in scarlet fever septic sore throat and streptococcal tonsillitis

Symptoms The incubation period varies from 1 to 10 days but is usually 3 to 5 days The illness begins abruptly in most cases with symptoms of feverishness chilliness headache and sore throat Nausea and vomiting are especially common in children A few patients complain of diarrhea Within a period of 24 to 48 hr the disease reaches its maximum intensity Chilliness is a constant symptom but true rigors are rarely observed Approximately 75 per cent or more of the patients complain of such constitutional symptoms as headache malaise and loss of appetite

The symptom which is very annoying and almost constantly present within 24 hr of onset is sore throat The soreness is aggravated by swallowing and may be referred to the neck so that even turning of the head is accompanied by pain Nasal obstruction and discharge are minor complaints but occur in 60 per cent of patients About half the patients develop very mild symptoms referable to the lower respiratory tract including cough and hoarseness The cough is not productive and is rarely associated with chest pain Loss of voice due to laryngitis does not occur Earache is common and may last a few hours to several days Occasionally epistaxis is observed

During the period of maximum temperature there may be a diffuse blush of the skin In some cases it becomes more pronounced and a diagnosis of *scarlet fever* is made The rash may appear from 1 to 5 days after onset of illness and is first noticed over the neck and upper chest It spreads rapidly to include the skin over the abdomen and upper and lower extremities The face appears flushed and a circumoral pallor is prominent in many cases Itching occasionally occurs but is rarely severe

Physical Signs The degree of prostration varies but the majority of patients appear mildly or moderately ill The temperature is usually elevated to 102 to 104 F occasionally it may be as high as 106 F A few patients have no fever In children the pulse rate is between 140 and 160 in adults between 120 and 140 per minute Usually the respirations are not greatly increased

Various degrees of diffuse redness of the mucous membranes of the posterior pharynx faucial tonsils and soft palate are invariably present The uvula is frequently edematous as are the tonsils and pharynx but to a lesser degree Lymphoid hyperplasia and edema which gives the posterior pharynx a cobblestone appearance are present Characteristically there is discrete to confluent exudate on the tonsils and variable numbers of pinhead size areas of exudate appear on the pharynx In severely ill patients the latter are seldom seen because nasal secretions cover the posterior wall The exudate is often yellow sometimes gray or white and is relatively easily removed by swabbing In about 20 per cent of adults and more frequently in infants exudative lesions on the mucous membranes do not develop Occasionally and especially if sinusitis and rhinitis are coexistent there is a thick mucopurulent nasal discharge which may be tinged with blood In children the nares may be excoriated The cervical lymph nodes are swollen and frequently tender The lymph nodes just below the angle of the jaw are the first to enlarge rarely they attain such size that the head is thrown back Marked adenopathy is frequently followed by suppuration

In those patients with *scarlet fever* the signs include both an enanthem and an exanthem The appearance of the throat is similar to that seen in tonsillitis and pharyngitis without rash except that diffuse redness is more intense and has been described as boiled lobster" red There may be punctate redness of the soft and hard palate The buccal mucous membranes appear red and swollen as do the lips About the second to fifth day small milk white patches may be seen on the buccal mucous membranes They represent desquamation of the epithelium and are easily peeled off

Early in the course of the infection the tongue is heavily coated and grayish Soon the tip and edges become an angry red Fungiform papillae become swollen and emerge through the gray surface of the tongue By the fourth to fifth day there is complete lingual desquamation which leaves multiple papillary elevations the so called "strawberry tongue

The color of the exanthem varies and has been described as scarlet bright red rose colored or dull dusky red At a distance there appears to be a uniform blush but upon close inspection innumerable small reddish points are seen Because of pin point elevations at the site of the hair follicles the skin may feel like sandpaper This sign is of special importance in races where the skin is heavily pigmented When the eruption is intense there may be many small miliary vesicles over the chest and abdomen The face may be free of rash but ordinarily the temples and cheeks are deep red leaving an area of pallor around the mouth and nose The rash is due to hyperemia and pressure causes it to fade In some areas there may be punctate hemorrhages which do not fade these are commonly seen in the creases at the elbow flexure (Pastia s sign) groin and axillary folds

nasal discharge persists it is usually indicative of sinus infection Individuals with this type of involvement may expel tremendous numbers of streptococci into their environment and thereby give rise to numerous secondary infections

The symptoms of acute streptococcal sinusitis other than purulent discharge are fever headache and pain The headache may be suboccipital when the sphenoid is involved or temporal and supra orbital when the ethmoid is involved Fever continuing after the fourth or fifth day of acute pharyngitis should suggest sinusitis There may be edema and redness over the maxillary or frontal sinuses and tenderness over those areas is elicited by slight pressure The diagnosis is established by culture of the discharge direct visualization of the nasal cavity and by transillumination and roentgenograms

A very common suppurative complication of streptococcal infections of the upper respiratory tract is involvement of the middle ear *Otitis media* may be unilateral or bilateral The two cardinal symptoms are fever and pain in the ear In a few adults and especially in children these symptoms may be absent Fever may develop suddenly and in the young is apt to be associated with nausea, vomiting loss of appetite and irritability The temperature tends to be irregular ranging between 102 and 103 F In older children and adults severe pain is almost invariably present Infants who can not complain of pain, may refuse to lie on the affected side or may pull the ear With involvement of the mastoid cells pain is intense and the fever is high

The physical signs of middle ear infection include tenderness around the ear inflammatory changes in the tympanic membrane and discharge The auricle itself sometimes is tender Early in the infection the tympanic membrane is injected and red later it may bulge at which time the landmarks become obliterated Finally if the process does not resolve rupture occurs

Mastoiditis usually arises in patients with otitis media but occasionally it may develop without an apparent infection of the middle ear The skin overlying the mastoid cells becomes red and swollen and the posterior wall of the external auditory canal may be involved The swelling may be so extensive that the auricle is pushed forward Early roentgenograms show no abnormalities but as the disease progresses cloudiness and destruction of the mastoid cells occur The continuation of fever in patients with a draining ear suggests mastoiditis Paralysis of the sixth cranial nerve and deep orbital pain indicate spread to the petrous cells Chills and septic fever suggest invasion of the blood stream thrombosis of the lateral sinus or meningitis

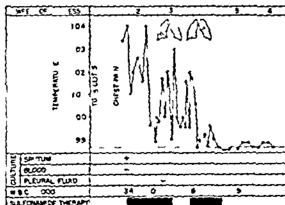


Fig 138 Streptococcal pneumonia with a sterile pleural effusion developing after an attack of acute tonsillitis

Peritonsillar Abscess

Complications of streptococcal sore throat are cellulitis and abscess formation around the tonsils In young children these lesions appear in the retropharyngeal areas Although these complications not infrequently follow a Lancefield group A infection similar abscesses may be caused by other organisms Characteristically the patient recovers from the acute throat infection only to complain a few days later of soreness on swallowing and difficulty in opening the mouth Trismus is caused by edema and spasm of the pterygoid muscles Fever may recur but in some instances it is absent Examination early in the course of illness shows diffuse redness and edema of the anterior pillar the tonsillar fossa, and the soft palate on the involved side As the disease progresses abscess formation may become apparent, and an area of fluctuation may be felt at the superior pole of the tonsil At this time the pain is intense Spontaneous rupture or surgical drainage is followed by rapid relief of symptoms

Pneumonia and Empyema

The natural course of pneumonia caused by Lancefield group A streptococci is extremely variable probably because in many instances it is secondary to such infections as influenza tonsillitis measles and erysipelas It may be associated with pneumococcal infection of the lung or may arise as a metastatic complication of streptococcal bacteremia Although it is not a common complication of streptococcal sore throat, about 25 per cent of pneumonia cases follow this infection (Fig 138) Characteristically this organism produces an interstitial or confluent pneumonia The reported mortality rate varies from 15 to 60 per cent

The onset of pneumonia may be abrupt, with such constitutional symptoms as chills feverishness anorexia and vomiting Symptoms include cough expectoration of purulent sputum, and chest pain

plate it is impossible to be sure whether the patient is a carrier or actually has an infection due to the streptococcus In such cases it is of considerable help to obtain acute and convalescent blood specimens for determination of the antistreptolysin titer

When a rash is associated with the above clinical and laboratory findings the diagnosis is scarlet fever Confirmation is obtained if later the skin desquamates Occasionally however the diagnosis is doubtful and in such cases the Schultz Charlton test may be of considerable aid In this test 0 1 ml scarlet fever antitoxin or 0 2 to 0 5 ml scarlet fever convalescent serum is injected subcutaneously into the area of the skin where the heaviest rash appears If the rash is due to the erythrogenic toxin blanching is observed within 2 to 8 hr The test should be employed soon after the eruption appears because blanching may not occur after the second day of rash The Dick test may also be of some use in establishing the diagnosis early in the disease it is positive whereas during convalescence it usually becomes negative

Nonbacterial exudative tonsillitis and pharyngitis must be differentiated from streptococcal infections of the oropharynx (see p 1044) The agents responsible for these infections have not been completely defined but it is known that some of the adenoviruses will produce respiratory infections associated with exudative lesions and in some outbreaks there is involvement of the conjunctiva In general the onset of illness is not rapid soreness of the throat is seldom marked and constitutional symptoms are mild Hoarseness and cough are likely to occur several days after the onset The exudate is rarely confluent Diffuse redness and edema of all the mucous membranes are rare The lymph nodes may be slightly enlarged but they are not remarkably tender

The leukocyte count is usually normal, although in a few cases it may be slightly elevated Cultures of the throat fail to show beta hemolytic streptococci Occasionally a few streptococci are recovered but these organisms usually belong to groups other than A and occur only in small numbers

Infectious mononucleosis is most frequently observed in young adults and because of the local reaction in the throat is likely to be confused with streptococcal pharyngitis (see p 1151) The onset may be insidious and malaise is prominent Sore throat with exudative lesions of the tonsils is observed in over half the cases The exudate is usually white and pasty and persists for 1 to 3 weeks The temperature tends to be very irregular and fever continues for a longer period than is usual in streptococcal infections Lymph node enlargement is more generalized but suppuration is not observed The spleen may be palpable In 10 to 15 per cent of cases a fleeting skin rash occurs which may be identical with that seen in scarlet fever In such cases a negative Schultz Charlton test may be helpful The blood changes are characteristic and a positive heterophil antibody test is usually obtained

Vincent's angina is not easily confused with streptococcal infections The disease is characterized by insidious onset without constitutional symptoms Fever is rare The area surrounding the exudate shows little inflammatory reaction and only one tonsil is involved Cervical adenopathy is usually unilateral

In contrast to streptococcal pharyngitis the onset of *diphtheria* is rarely sudden and the symptoms are not severe (see p 919) Sore throat is not a constant feature of the disease The exudate is smooth and cream colored and appears to be incorporated in the mucous membranes The membrane is removed with difficulty leaving a bleeding bed Cutaneous rashes are absent Cultures show *Corynebacterium diphtheriae*

In patients with a rash the disease must be differentiated from *German measles* and *measles* In German measles the posterior cervical lymph node enlargement is helpful as well as the fact that the rash tends to be macular and discrete The tongue never peels and a leukopenia is characteristic In measles there are prodromal respiratory symptoms and the maculopapular rash occurs chiefly on the face and neck There is no blanching of the skin following a Schultz Charlton test The presence of Koplik's spots aids in establishing the diagnosis

Streptococcal infections without exudate or a cutaneous rash must be differentiated from *influenza virus infections* and *common respiratory diseases* In general such differentiations cannot be made on clinical evidence alone so that the leukocyte count culture studies and serologic tests must be employed

Primary *herpes simplex pharyngitis* (see p 1092) and *herpangina* (see p 1091) are characterized by vesicles which rupture and produce small ulcers covered with exudate Herpetic lesions are scattered over all mucous membranes of the mouth and the kissing ulcer under the tip of the tongue is typical The ulcers of herpangina caused by Coxsackie A viruses are observed on the anterior pillars and the soft palate In both diseases the leukocyte count is usually normal

Sinusitis Otitis Media and Mastoiditis

Some degree of *sinusitis* probably occurs in every patient with streptococcal infection of the throat Aside from a purulent rhinitis which persists for a few days there are usually few symptoms or signs of involvement of the paranasal sinuses When the

the skin and to a lesser extent of the mucous membranes The onset is usually abrupt beginning after an incubation period of approximately 1 to 4 days In some patients a history of preceding respiratory infection is obtained The initial symptoms include chilliness feverishness headache malaise anorexia and vomiting The first symptom may be a true rigor At the onset the local cutaneous lesion may not be apparent although there may be slight redness in those instances where it arises in conjunction with an abrasion of the skin The skin may itch and feel sore around the point of entry of the organisms Within a few hours and usually by 24 hr the cutaneous lesion becomes obvious

The skin of the face is most commonly involved but any area of the body may be infected The point of entry around the face may be just anterior to the ear at the inner canthus of the eye around the lips and nose or over the cheeks From these points the lesion spreads rapidly reaching its maximum extent within 3 to 6 days On the face erysipelas frequently involves the butterfly area i e the cheeks and nose The lesion consists of an advancing border which is raised from the surrounding normal skin and may be purple Within this border the skin is tense and usually a dark dull red If the infection occurs in areas where the skin is lax such as around the eyes edema is pronounced The eyelids frequently become so swollen that they cannot be opened Blebs or even necrotic areas may appear as the disease progresses

At the height of the infection the temperature is usually high (104 to 105 F) although occasionally the febrile response is slight The blood stream is not uncommonly invaded during this period The disease lasts for a variable length of time but in most instances recovery is apparent by the sixth to seventh day The local lesion begins to fade in the center and is usually accompanied by some desquamation and pigmentation No scarring results unless abscesses develop

Before the introduction of chemotherapy the fatality rate was about 15 per cent During the first 6 months of life approximately 65 per cent succumb whereas in children and young adults the death rate is low In patients with fatal infections the lesion is likely to involve the trunk and in addition the blood stream is invaded

Bacteremia

Streptococci are a common cause of bacteremia but in uncomplicated tonsillitis and pharyngitis the organisms rarely invade the blood stream Bacteremia occurring under the age of twenty usually is secondary to otitis media mastoiditis or thrombosis of the lateral or cavernous sinuses In the adult invasion of the blood stream is especially likely to occur in women with puerperal infections whereas after the age of forty bacteremia is usually secondary to cellulitis and erysipelas Metastatic abscesses develop infrequently during the course of bacteremia

The diagnosis of bacteremia is difficult and can be made only by culturing the organisms from the blood The sudden development of chills and high fever either irregular or continuous suggests invasion of the blood stream Severe headache nausea vomiting and delirium are common symptoms In streptococcal bacteremia there may be arthritis signs of pneumonia petechiae or skin eruptions In fulminating cases anemia develops rapidly and jaundice may occur Without specific therapy the mortality rate is 70 per cent

Pyelonephritis

Infections of the kidney and urinary passages are discussed in detail in Chap 144 (p 967) Here it should be emphasized that streptococci usually belonging to group D may be isolated from the urine of patients with infection of the urinary tract When the organisms are present in large numbers there is usually dysuria frequency flank pain fever and pyuria

Treatment

There are now several agents which may be employed in the therapy of aerobic streptococcal infections The sulfonamides have been widely employed These compounds exert a bacteriostatic effect against all Lancefield groups except D However there are strains of group A streptococci that have acquired resistance Most antibiotic compounds exhibit a more marked effect than the sulfonamides but penicillin displays the maximal antistreptococcal activity Penicillin actually kills group A organisms and if it is administered for at least 10 days all streptococci are eliminated in most instances Therapeutic measures which do not result in the eradication of the infecting organism do not alter the attack rate of rheumatic fever

The administration of penicillin or other antibiotics within 24 hr of the onset of streptococcal respiratory infections results in a definite favorable effect on the symptoms and signs associated with the acute illness When therapy is instituted after 18 hr a favorable effect is difficult to demonstrate but suppurative complications including sinusitis otitis media and peritonsillar cellulitis are still prevented The time that treatment is started is not decisive in the reduction of rheumatic fever however early therapy may be important in the prevention of nephritis

In the average case of streptococcal infection, whether scarlet fever tonsillitis or erysipelas sufficient concentration of antibiotic can be maintained most readily by a single injection of 600 000 to

The pulse and respiratory rates are increased and cyanosis may be prominent The temperature tends to be high (104 F) and septic in type Examination reveals local signs of pneumonia with scattered fine rales and occasional areas of dullness Frank signs of lobar consolidation are rare

The leukocyte count is almost invariably elevated to 20 000 to 30 000 and the sputum is found to contain large numbers of group A organisms Usually the blood cultures are sterile when bacteremia occurs the prognosis is poor

The untreated disease runs a variable course In most instances recovery is delayed for several weeks and lung abscess and bronchiectasis are not uncommon complications In fatal cases mediastinitis and pericarditis may occur The most frequent complication is empyema which occurs in 20 per cent of the cases

Streptococcal *empyema* is usually secondary to pneumonia caused by the same organism but occasionally it arises following other infections of the lung infarcts or lung tumors It is most likely to occur under the age of thirty years and the mortality rate in untreated cases is high Early in the disease the pleural fluid may be hemorrhagic It becomes thick and purulent slowly in contrast to the exudate seen in pneumococcal empyema

Pericarditis Arthritis Peritonitis and Meningitis

Streptococcal infections of the various body cavities result from bacteremia or from extension from a local lesion *Pericarditis* a rare complication is especially likely to occur during the course of pneumonia or empyema The diagnosis is difficult since the symptoms arising from pericarditis are overshadowed by the primary disease The first sign may be a sudden increase in pulse rate and the development of an audible pericardial friction rub Roentgenograms are of great aid in establishing the diagnosis Once the diagnosis is suspected aspiration and culture of the fluid are indicated

Suppurative arthritis is secondary to bacteremia or to extension of a local cellulitis It is a rare complication of streptococcal sore throat Pain is the most common symptom and usually only one joint is involved The pain is first noticed on motion but within a short period redness swelling and tenderness develop and the pain becomes intense Aspiration reveals a fluid containing polymorphonuclear leukocytes and streptococci Nonsuppurative arthritis is seen in patients with scarlet fever during the first week of illness

Infection of the peritoneum with the hemolytic streptococcus is rare but is especially apt to be associated with such local infections as erysipelas and scarlet fever In these cases the organism belongs to Lancefield group A Symptoms develop rapidly and in addition to fever and other constitutional symptoms prostration abdominal pain and vomiting are prominent The pulse is rapid and weak The abdomen is distended tender and rigid to palpation

Streptococcal *meningitis* is usually caused by group A organisms but occasionally members of other groups may be isolated from the spinal fluid In most instances the meningitis arises by extension and invasion of the blood stream from an otitis media mastoiditis or petrositis which are especially likely to develop following infection of the respiratory tract and are most frequently seen in the young age groups Prior to the introduction of specific therapy these infections were always fatal The symptoms of streptococcal meningitis are not distinguishable from other types of bacterial meningitis It should be emphasized that all patients especially infants with infections of the middle ear should be watched for signs of meningeal irritation Once such signs develop lumbar puncture and culture of the spinal fluid establish the diagnosis

Wound and Skin Infections Lymphangitis Puerperal Fever and Erysipelas

As indicated earlier *wound and skin infections* are usually the result of contamination Children with chickenpox impetigo and other skin lesions may become infected with group A and C streptococci

Hemolytic streptococci are responsible for the majority of cases of the familiar form of *lymphangitis* The disease is characterized by the rapid development of one or more fine red streaks extending upwards from the hand or foot Usually the process continues up to the axilla or groin and the lymph nodes in these areas become enlarged and tender Associated with the spread of the infection in the lymphatics such symptoms as rigor fever malaise headache and vomiting occur Occasionally the blood stream is invaded The original site of infection in these cases of lymphangitis may be unapparent Although these infections may be serious the course of the illness is usually short and suppuration seldom occurs along the course of the lymphatics or in the regional lymph nodes

Puerperal infections caused by hemolytic streptococci are always serious Following abortion or delivery the streptococci invade the endometrium and lymphatics The infection may spread to the surrounding structures producing cellulitis phlebitis abscess peritonitis or bacteremia The patient develops a high irregular fever associated with rigors The pulse is rapid The diagnosis is based on local signs of infection as well as on such laboratory findings as leukocytosis and isolation of streptococci from the blood stream or from the cervical discharge

Erysipelas is an acute streptococcal infection of

phylaxis when given to populations already experiencing an epidemic will control the outbreak as long as the drug is administered When therapy is stopped streptococcal infections again occur because of the failure of sulfonamides to eliminate the infecting organism For this reason oral penicillin in doses of 250 000 units two or three times daily for 10 days or the injection of 1 200 000 units of benzathine penicillin are preferred forms of prophylaxis in large population groups Benzathine penicillin in doses of 600 000 and 1 200 000 units will protect the individual from new infections for from 3 and 4 to 6 weeks respectively

Tonsillectomy has been employed widely as a prophylactic measure for streptococcal infections *It is obvious that tonsillitis cannot occur if the* organ is removed but there is no protection afforded against streptococcal pharyngitis Indeed the only measurable effect is that tonsillectomy makes subsequent recognition of the cause of the respiratory illness difficult

Many attempts have been made to control respiratory disease by altering certain environmental factors by using for example ultraviolet light aerosols and various dust holding procedures and by treating bed clothing with oils It has been demonstrated that such methods decrease the contamination of the air but the degree of their effectiveness in preventing infection is slight

Several local infections of various organs require special comment Erysipelas is difficult to control In the few patients who have repeated attacks the prophylactic use of sulfonamides would be justified Wound infections and puerperal sepsis are best prevented by good surgical aseptic techniques and the avoidance of unnecessary examinations

LATE NONSUPPURATIVE COMPLICATIONS OF GROUP A STREPTOCOCCAL INFECTIONS

As indicated previously beta streptococcal infections assume importance not only because of the high morbidity and the immediate suppurative complications but also because of the late sequelae There is considerable evidence that rheumatic fever acute glomerulonephritis and scleredema adultorum (see p 1706) are precipitated by if not directly related to infection with the beta streptococcus Rheumatic fever may be followed by valvular disease and therefore this sequela of streptococcal infection assumes importance as a cause of chronic illness

Etiology and Pathogenesis

Although group A streptococci are considered to be the inciting agent of both rheumatic fever and glomerulonephritis these two diseases have never been reproduced in animals nor have the mechanisms involved been defined Therefore it is not surprising that numerous theories have been proposed to explain the nature of the cardiac and renal complications

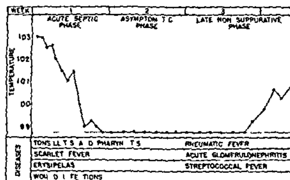


Fig 139 The various phases of hemolytic streptococcal infections

Streptococcal infections are characterized by an acute toxic or septic phase which lasts from 3 to 7 days Following the acute illness the patient seemingly recovers completely except for those few individuals who have developed a suppurative complication After a latent period (termed *phase II* by Coburn) the patient may again present symptoms and signs of illness but this time the manifestations are related to involvement of new areas of the body and the illnesses developing after the latent period present a varied clinical picture These illnesses have been collectively termed the late nonsuppurative complications of hemolytic streptococcal infections (Fig 139) The latent period and the resemblance of certain manifestations to serum sickness suggest some altered or unusual tissue reaction but to ascribe hypersensitivity as the responsible mechanism on the basis of this evidence alone is not warranted

The spectrum of the nonsuppurative illnesses is broad Certain patients develop fever with no localizing signs Others exhibit lymphadenitis with fever Such illnesses have been called streptococcal fever but it seems probable that they represent mild rheumatic attacks Approximately 3 per cent develop signs of involvement of the joints or heart and a diagnosis of rheumatic fever is evident In a few depending on the serologic type of infecting streptococcus acute glomerulonephritis becomes manifest Skin eruptions such as erythema marginatum erythema nodosum and scleredema adultorum occasionally appear

This sequence of (1) an acute streptococcal respiratory illness (2) a latent period of 1 to 5 weeks and (3) the development of nonsuppurative illness occurs with sufficient frequency to suggest a causal relationship to the group A *streptococcus* In the family unit experiencing streptococcal in

900 000 units of benzathine penicillin Another method is the intramuscular administration of 600 000 units of procaine penicillin in 2 per cent aluminum monostearate in oil every 2 or 3 days for three injections In patients who exhibit rheumatic heart disease and who develop a streptococcal infection it may be advisable to administer 600 000 units of procaine penicillin twice daily for 2 weeks

Oral therapy may be prescribed but it should be emphasized that many patients discontinue the medication when the acute phase symptoms subside Under these circumstances the organism frequently invades the tissues again and a clinical relapse occurs More important the attack rate of the nonsuppurative complications is not altered All forms of oral medication must be taken in full doses for at least 10 days and preferably for 2 weeks Oral preparations of penicillin are given in doses of 250 000 units four times daily If the patient is sensitive to penicillin then erythromycin in doses of 0 2 Gm is administered every 6 hr Tetracycline is given every 4 hr in a dose of 0 25 Gm Chlortetracycline and oxytetracycline may also be employed

The *sulfonamides* should never be employed in the treatment of streptococcal infections since they fail to eliminate the infecting organism and do not alter the subsequent attack of rheumatic fever Application of penicillin or other drugs by means of troches or sprays has little effect on the local inflammatory lesion or on the infecting organism

Penicillin appears to exert a definite effect on the suppurative complications of tonsillitis and pharyngitis Penicillin treatment of otitis media is followed by a gradual decrease in the amount of exudate redness of the drum disappears and within 4 to 14 days there is no further aural discharge The temperature if elevated returns very rapidly to normal Complications such as mastoiditis are rare during this form of therapy If treatment is instituted before aural discharge occurs the drum membranes must be watched closely A tympanic cavity filled with purulent exudate requires drainage In general it is wise to continue penicillin treatment for several days after all discharge has ceased and the temperature has returned to normal Premature discontinuance of treatment may lead to a recurrence It is perhaps important to emphasize that staphylococcal infections of the middle ear are common in patients with group A streptococcal infections of the throat and in these cases discharge is likely to be prolonged

Infections of the mastoid and paranasal sinuses should likewise be treated by the parenteral administration of penicillin Streptococcal pneumonia should be treated with somewhat larger amounts of penicillin a dose of 40 000 units every 3 hr is suggested From 30 000 to 50 000 units every 2 hr should be given to patients with puerperal sepsis and bacteremia Empyema purulent pericarditis and arthritis are best treated by local instillation of 10 000 to 50 000 units of penicillin every 48 to 72 hr until cultures are sterile In addition full doses of parenteral penicillin should be administered In these infections early treatment is required if surgical drainage is to be avoided

In patients developing localized collections of pus surgical drainage should be promptly established Surgery should not be injudiciously employed because of the danger of spread of the infectious process Patients with lymphangitis and arthritis should have the involved parts immobilized

General measures for the supportive and symptomatic therapy of infections should be employed The use of saline gargles and irrigations of the throat may be effective in the relief of the angina associated with tonsillitis The use of cold applications to erysipelas or to tender and enlarged cervical lymph nodes frequently affords symptomatic relief

Prevention

It may be stated that there is no completely adequate method for the prevention of streptococcal infections A number of procedures will limit the spread of the organism to some extent The problem is exceedingly complicated because group A streptococci occur in the upper respiratory tract of many individuals

In the past it has been customary to isolate all patients with scarlet fever but today such procedures seem unwarranted for no precautions are taken for sore throat without a rash caused by the same bacterium Any patient with a streptococcal infection of the upper respiratory tract may be a source of infection During the acute stage of all such illnesses the patient should be advised against intimate contact with others

Approximately 90 per cent of patients with streptococcal infections continue to carry the organism in the pharynx 3 months after the acute infection Usually the number of organisms is small Individuals with suppurative complications of the sinuses are likely to harbor large numbers of streptococci and would appear to be a dangerous source of infection Proper therapy of acute infections with penicillin prevents the development of the carrier state

There is no specific immunizing procedure which will protect against streptococcal infections This is not surprising since the evidence today is that immunity is largely type specific

Individuals or groups of individuals may be protected from streptococcal infections by the prophylactic use of sulfonamide drugs For this purpose 1 Gm sulfadiazine is administered daily Such pro

these nephritogenic strains is not constant suggesting that either the strains vary in their nephritogenic capacity or some other factor is operative Since the attack rate may approach 90 per cent following infection multiple cases within the family unit are common

Pathology

Rheumatic Fever

The tissue changes occurring during the course of rheumatic fever are found in the fibrous tissues located throughout the body The pathologic changes are widespread but because alterations in certain organs result in abnormal function the clinician and the pathologist have been especially interested in the changes occurring in the heart joints and brain The characteristic change evoked by acute rheumatic fever is the development of minute nodules called *Aschoff bodies* This lesion is considered specific for rheumatic fever The Aschoff nodule develops as a result of swelling and fusion of the collagenous ground substances of the connective tissues Around these areas which are usually oval or spindle shaped there may be collections of lymphocytes and occasionally polymorphonuclear leukocytes As the lesion ages fibrosis occurs leaving a minute scar

In patients dying with acute rheumatic myocarditis the heart shows few gross abnormalities The left ventricle is enlarged and there is widening of the atrioventricular valves The leaflets of the mitral valve may be slightly swollen and thickened and along the point of contact of the cusps a row of small beadlike vegetations is observed In patients with pericarditis there may be fluid in the pericardial sac and the heart may be covered with a fibrinous exudate

Microscopic examination reveals small areas of inflammation scattered throughout the myocardium These Aschoff nodules are especially prominent in the base of the interventricular septum and beneath the endocardium of the left atrium It is easy to visualize that these lesions associated with an inflammatory reaction give rise to alterations in the conductive mechanism of the heart

The endocardial lesions are most frequently found in the valves and the left atrium In the valve leaflets there is edema and subendothelial infiltration by lymphocytes and occasionally by polymorphonuclear leukocytes The endothelium is damaged and it is in these areas that fibrin is deposited producing the beadlike vegetations The chordae tendineae are also involved in this inflammatory process As the disease continues fibrosis develops with subsequent contraction of the tissues producing the valvular deformities characteristic of chronic rheumatic heart disease

The joints become red swollen and tender The periarticular tissues and synovia are edematous and show collections of mononuclear cells The synovial fluid becomes increased Involvement of the tendons especially the hamstring and Achilles tendons gives rise to the so called "growing pains" of childhood Subcutaneous nodules loosely connected to the tendon sheaths are likely to be found during the acute phase of the disease in children

In the brain true Aschoff bodies are seldom observed instead there is a perivascular collection of round cells There may be proliferation of the intima and thrombosis of vessels

Inflammatory reactions have been described in the tissues of other organs of the body In the lung there may be an interstitial pneumonia and hemorrhage

Acute Glomerulonephritis

The kidneys are normal or slightly enlarged and appear pale Over the surface small punctate hemorrhages are observed Histologically the earliest lesion is an increased cellularity of the glomerulus with infiltration with polymorphonuclear cells Red cells and leukocytes appear in Bowman s space and in the tubules The basement membrane is thickened The tubular cells may show some swelling Acute fibrinoid necrosis of the arterioles and glomerular tufts is seen Lesions observed at autopsy after several weeks or months of illness show epithelial crescents fibrinoid necrosis tubular degeneration and inflammatory infiltration around the glomerulus Fibrosis is a late manifestation The relation of these latter changes to nephritis following group A infections has not been well defined

Acute Rheumatic Fever

Clinical Manifestations One of the outstanding characteristics of the late nonsuppurative complications of streptococcal infections is the variation of the clinical features Frequently a definite diagnosis of rheumatic fever is easily made but there are also many instances where such a diagnosis is difficult if not impossible The correct diagnosis may become apparent only after a long period of observation

Streptococcal fever is a term applied when there is fever usually of mild degree without other signs of rheumatic activity or of a suppurative process A history of a preceding pharyngitis is usually obtained There may be some cervical lymphadenitis but in many instances the glands are not prominent or tender In some patients the temperature may be normal except during the late afternoon An increase in the total leukocyte count or in the sedimentation rate may accompany the fever

Rheumatic fever may be insidious in onset or it may develop rapidly Although it is common for

fections in patients with scarlet fever and in food and milk borne outbreaks it is not uncommon to observe rheumatic fever and nephritis Other non bacterial respiratory infections are not followed by these complications

Further evidence that rheumatic fever and nephritis are related to group A streptococcal infections is obtained from study of patients with these diseases Usually a history of a recent infection of the throat is obtained and cultures frequently exhibit hemolytic colonies Antistreptolysin titers of the serum are elevated Measures known to protect the individual from streptococcal infections reduce the incidence of rheumatic fever and nephritis

The exact mechanism whereby rheumatic fever and acute glomerulonephritis are produced is not known The majority of students favor some form of hypersensitivity mechanism but it is now apparent that the substances responsible for the tissue reactions are not identical in nephritis and rheumatic fever Furthermore the host response to infection with the streptococcus in patients with nephritis is different from that in patients with rheumatic fever in the first instance a recurrence is rare in the second it is common In nephritis the observation that hematuria is observed during the acute streptococcal illness suggests the direct action of some nephritotoxic substance however the hematuria clears and subsequently becomes apparent again In rheumatic fever and to a less extent in nephritis the patient responds to the initiating infection by the production of large amounts of antibody to various streptococcal antigens Why such a response is more likely to be associated with a nonsuppurative complication is unknown but *this observation contributes to the interest in the* antigen antibody reaction in relation to the mechanisms involved in tissue damage

In experimental models tissue reactions in the kidneys and to a less extent in the heart have been produced by a variety of procedures These observations have contributed to the emphasis on altered reactivity of the tissues but it is difficult to translate these studies to the diseases nephritis and rheumatic fever as they occur in man Indeed in cases of rheumatic valvular heart disease there is some evidence indicating that the streptococcus produces its damage directly Green and others have recovered hemolytic streptococci from the valves of patients dying with acute rheumatic fever

Epidemiology of Rheumatic Fever and Nephritis

There are no reliable figures of the incidence of rheumatic fever and glomerulonephritis because the diseases are not reportable and in many instances their manifestations are so mild that the illnesses are not recognized That rheumatic fever occurs frequently is indicated from reports which show that approximately 2 to 3 per cent of patients with streptococcal infections subsequently develop rheumatic fever Since most people experience one to several streptococcal infections in a lifetime it can be assumed that rheumatic fever is common but frequently goes unrecognized More accurate information is available from studies of heart disease 1 to 6 per cent of the population exhibit specific valvular defects Since many patients with rheumatic fever recover completely such high rates of valvular defects must represent many cases of rheumatic fever in the population In contrast to rheumatic fever attack rates for nephritis following streptococcal infections vary from 0 to 90 per cent. Determination of the number of cases of chronic nephritis gives no indication of the past experience of the population with the acute disease or with streptococcal infections since the relationship of the chronic disease to the streptococcal infection is not clear

Rheumatic fever occurs with equal frequency in the two sexes whereas clinical manifestations of nephritis are observed more frequently in the male Both complications occur primarily between the ages of two and thirty with a peak of incidence at seven Nephritis is somewhat more frequently observed in the young infant than rheumatic fever Acute rheumatic fever in the adult is likely to be a recurrence rather than an initial attack Age does not alter susceptibility to rheumatic fever but streptococcal infections are less likely to be acquired in adult life

Individuals who have experienced one attack of rheumatic fever are especially susceptible to subsequent attacks It has been estimated that as many *as 40 per cent of patients will experience a recur*rence within 1 year after the initial attack However as time progresses the risk of recurrence decreases

Wilson has stated that the attack rate of rheumatic fever in siblings of rheumatic parents is higher than in siblings of parents free of the disease but recent data show that following a streptococcal infection the attack rate is 3 per cent irrespective of the presence or absence of the rheumatic state in the parents These results would indicate that there is no increased susceptibility to rheumatic fever in such families

The other epidemiologic features of acute rheumatic fever and acute nephritis are those of streptococcal infections in general In addition the epidemiology of nephritis is governed by the fact that not all strains of group A streptococci are capable of producing renal disease The evidence at present indicates that strains belonging to type 12 account for the majority of cases throughout the world In addition strains of type 4 25 and a newly recognized type termed *Red Lake* may produce nephritis The attack rate of nephritis following infection with

One of the most characteristic features of rheumatic fever is the development of *subcutaneous nodules* These nodules which vary in size from 1 mm to 2 cm are especially likely to develop over the extensor tendons of the hands and feet over the extensor aspects of the knee and elbow and over the spine scapulas and skull Usually they are distributed symmetrically and may occur in crops They lie deep in the tissue and the skin is movable over their surfaces They are not painful Detection of these nodules is best accomplished by inspection of the skin when drawn taut by flexion of the joints The nodules persist for a few days to several weeks but always disappear Since subcutaneous nodules are especially likely to develop in patients with severe carditis they are seldom helpful from the standpoint of diagnosis

The tendency toward *recurrent attacks* is a striking feature of rheumatic fever Approximately three fourths of all patients with recognizable rheumatic fever will develop a recurrence of the disease so that a previous history of an attack aids in the establishment of the proper diagnosis

Numerous symptoms physical signs and abnormalities in laboratory examinations aid in the establishment of proper diagnosis *Fever* is usually associated with acute rheumatic fever although it may be absent in patients with chorea Fever may be the only clinical manifestation of the disease other studies such as serial electrocardiograms and detection of endocardial murmurs being required to establish the diagnosis A diagnosis of rheumatic fever made solely on the basis of low grade fever is not warranted but it should be emphasized that fever may be the only sign of rheumatic activity

Little experience is required to appreciate the protean character of rheumatic fever Studies of outbreaks of streptococcal infection emphasize that nonsuppurative sequelae include typical rheumatic fever and a low grade often continuous fever without signs of rheumatic activity It is natural to assume that such cases of so called streptococcal fever are produced by the same mechanism responsible for the clinically recognizable form of rheumatic fever A history of a preceding streptococcal infection is of help in diagnosis (Fig 140)

During the acute phase of rheumatic fever various *rashes* may appear Most typical is *erythema marginatum* This rash is said to occur in 15 per cent of patients with acute rheumatic fever and probably should be considered indicative of active rheumatic infection It is characterized by a depressed center and an erythematous margin which may form rings When the lesions fuse various gyrate patterns are observed The rash is evanescent and may become apparent only by warming the body Other rashes include erythema nodosum urticaria and various purpuric lesions

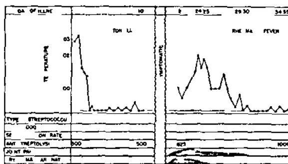


Fig 140 The time sequence of streptococcal tonsillitis and rheumatic fever

Abdominal pain occurs frequently and may be incorrectly diagnosed as resulting from acute appendicitis Since a leukocytosis occurs in both rheumatic fever and appendicitis operation is frequently performed Careful search for other signs of rheumatic activity should be made in all children and young adults complaining of abdominal pain and fever

Not only does abdominal pain occur as a manifestation of acute rheumatic fever but also pleuritic pain is observed *Pleurisy* is usually associated with severe rheumatic fever and gives rise to pain on respiration Rarely it is the initial manifestation of the illness Usually the pleurisy does not persist for more than a few days and symptoms may be relieved as fluid accumulates in the intrapleural space In some patients and again especially in those with a severe illness symptoms and signs of *pneumonia* may develop The sputum may become blood streaked Physical signs are frequently difficult to interpret for there is usually concomitant myocarditis and cardiac failure Roentgenographic examination of the lungs is a most valuable procedure in patients suspected of having pneumonia

Epistaxis is commonly observed in patients with acute rheumatic fever The exact cause of these recurrent attacks of bleeding is not known Hypoprothrombinemia may be due to salicylate administration

Laboratory Findings The urine is usually normal Traces of albumin may occur during the febrile period and microscopic hematuria is observed on occasion In patients with severe or prolonged infections various degrees of anemia are common A leukocyte count of from 15 000 to 30 000 is *the rule* during the acute phases of infection but in some patients the count may be normal

The sedimentation rate is an excellent index of rheumatic activity and is generally considered more reliable than the leukocyte count The rate of *sedimentation* of the cells almost invariably increases during the acute phases of the infection *with clin*

ients to give a history of a preceding strepto ocal respiratory infection followed by a latent riod of from several days to 6 weeks occasionally nptoms of rheumatic fever develop without a ent symptom free period Usually the patient nplains of *malaise which is soon followed by fev* ishness perspiration prostration and polyar itis

In the absence of a specific diagnostic test the ognition of rheumatic fever depends upon the esence of a combination of symptoms and signs which the most important are polyarthritis car is chorea subcutaneous nodules erythema mar iatum fever and dramatic improvement of pain d fever following the administration of salicylates is important to stress that many of these mani tations may be absent in a given instance

Although *migratory polyarthritis* is considered e of the typical symptoms of rheumatic fever it also a confusing symptom since arthralgia may caused by other diseases In rheumatic fever inful joints develop rapidly and the ankles knees ps shoulders elbows and wrists are likely to be olved Occasionally the small joints become in med Several joints may become involved simul ieously or they may be affected in rapid succes n As one joint becomes involved the pain and elling in another may be receding Arthralgia in y one joint may last from a few hours to several ys or rarely weeks Commonly there are all the ;ns of acute inflammation with redness swelling at pain and tenderness

In children arthritis may be atypical the mani itations being pain and tenderness without elling of the joint The arthritis of rheumatic er does not suppurate and normal function is itored following subsidence of symptoms and ;ns of inflammation

Death during the course of acute rheumatic fever due to active *carditis* Patients with severe cardiac volvement appear prostrated and pale the fever apt to be high the pulse is rapid and weak and ere may be associated symptoms and signs of ilure of the heart A few patients complain of ecordial discomfort and more rarely of severe un The diagnosis of active carditis is established most patients only after careful examination in uding the use of the electrocardiogram

The single sign indicative of involvement of the idocardium is a murmur The most common mur ur associated with the initial attack is the mitral stolic which in some patients is associated with soft aortic diastolic murmur The mitral systolic urmur may be functional in origin Those mur urs which vary little with respiration persist in irious body positions with maximum intensity at ie apex are high pitched occur throughout most f systole and persist during the period of observation should be considered indicative of endocarditis The faint systolic murmur localized to the apex which is heard only while the heart rate is rapid is usually functional in origin Unimportant murmurs frequently disappear as the patient im *proves During the phase of acute carditis* a mid diastolic rumble may be heard at the apex In patients with preceding rheumatic infections a mitral diastolic or presystolic murmur indicates rheumatic heart disease

Cardiac enlargement is frequently encountered in children but seldom observed in the adult The diagnosis of involvement of the myocardium is usually based on the recognition of disturbances of rhythm and electrocardiographic abnormalities Most patients with rheumatic fever if examined frequently will show evidence of myocardial in volvement Tachycardia is frequent Gallop rhythm usually heard during the acute phases of the ill ness is especially apt to occur The heart sounds may be muffled or the first sound may vary in intensity The finding of dropped beats suggests a partial heart block (Wenckebach phenomenon) Auricular fibrillation uncommon in children may be associated with recurrent attacks of rheumatic fever in the adult

The electrocardiographic change most frequently encountered during the course of acute rheumatic fever is prolongation in the P R interval This inter val usually becomes normal as signs of infection disappear but prolongation may persist Other ab normalities include partial auriculoventricular heart block auriculoventricular dissociation inversion of T waves and bundle branch block

Discomfort over the precordial area does not always indicate acute pericarditis but the detection of a harsh to and fro friction rub is pathognomonic Frequently the precordial pain is severe in pa tients exhibiting a friction rub Rheumatic peri carditis in children is often associated with little pain Effusion into the pericardial sac may develop and must be differentiated from cardiac dilatation

One of the major manifestations of rheumatic fever is *chorea* or St Vitus dance In children it is observed in approximately one half the patients whereas in adults it is rare Commonly chorea ap pears late in the illness so that it may be the only manifestation of the rheumatic state Chorea usually develops slowly so that a week or two is required before the parents realize the child is ill Typically the patient is restless nervous and emotionally un stable and performs many purposeless movements The manifestations of chorea are usually mild and careful observation is required to detect the in coordination Hyperextension of the fingers grimac ing and purposeless movements of the tongue ex tremities and fingers are characteristic (see p 249)

One of the most characteristic features of rheumatic fever is the development of *subcutaneous nodules* These nodules which vary in size from 1 mm to 2 cm are especially likely to develop over the extensor tendons of the hands and feet over the extensor aspects of the knee and elbow and over the spine scapulas and skull Usually they are distributed symmetrically and may occur in crops They lie deep in the tissue and the skin is movable over their surfaces They are not painful Detection of these nodules is best accomplished by inspection of the skin when drawn taut by flexion of the joints The nodules persist for a few days to several weeks but always disappear Since subcutaneous nodules are especially likely to develop in patients with severe carditis they are seldom helpful from the standpoint of diagnosis

The tendency toward *recurrent attacks* is a striking feature of rheumatic fever Approximately three fourths of all patients with recognizable rheumatic fever will develop a recurrence of the disease so that a previous history of an attack aids in the establishment of the proper diagnosis

Numerous symptoms physical signs and abnormalities in laboratory examinations aid in the establishment of proper diagnosis *Fever* is usually associated with acute rheumatic fever although it may be absent in patients with chorea Fever may be the only clinical manifestation of the disease other studies such as serial electrocardiograms and detection of endocardial murmurs being required to establish the diagnosis A diagnosis of rheumatic fever made solely on the basis of low grade fever is not warranted but it should be emphasized that fever may be the only sign of rheumatic activity

Little experience is required to appreciate the protean character of rheumatic fever Studies of outbreaks of streptococcal infection emphasize that nonsuppurative sequelae include typical rheumatic fever and a low grade often continuous fever without signs of rheumatic activity It is natural to assume that such cases of so called streptococcal fever are produced by the same mechanism responsible for the clinically recognizable form of rheumatic fever A history of a preceding streptococcal infection is of help in diagnosis (Fig 140)

During the acute phase of rheumatic fever various *rashes* may appear Most typical is *erythema marginatum* This rash is said to occur in 15 per cent of patients with acute rheumatic fever and probably should be considered indicative of active rheumatic infection It is characterized by a depressed center and an erythematous margin which may form rings When the lesions fuse various gyrate patterns are observed The rash is evanescent and may become apparent only by warming the body Other rashes include erythema nodosum urticaria and various purpuric lesions

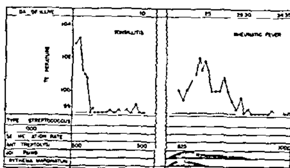


Fig 140 The time sequence of streptococcal tonsillitis and rheumatic fever

Abdominal pain occurs frequently and may be incorrectly diagnosed as resulting from acute appendicitis Since a leukocytosis occurs in both rheumatic fever and appendicitis operation is frequently performed Careful search for other signs of rheumatic activity should be made in all children and young adults complaining of abdominal pain and fever

Not only does abdominal pain occur as a manifestation of acute rheumatic fever but also pleuritic pain is observed *Pleurisy* is usually associated with severe rheumatic fever and gives rise to pain on respiration Rarely it is the initial manifestation of the illness Usually the pleurisy does not persist for more than a few days and symptoms may be relieved as fluid accumulates in the intrapleural space In some patients and again especially in those with a severe illness symptoms and signs of *pneumonia* may develop The sputum may become blood streaked Physical signs are frequently difficult to interpret for there is usually concomitant myocarditis and cardiac failure Roentgenographic examination of the lungs is a most valuable procedure in patients suspected of having pneumonia

Epistaxis is commonly observed in patients with acute rheumatic fever The exact cause of these recurrent attacks of bleeding is not known Hypoprothrombinemia may be due to salicylate administration

Laboratory Findings The urine is usually normal Traces of albumin may occur during the febrile period and microscopic hematuria is observed on occasion In patients with severe or prolonged infections various degrees of anemia are common A leukocyte count of from 15 000 to 30 000 is the rule during the acute phases of infection but in some patients the count may be normal

The sedimentation rate is an excellent index of rheumatic activity and is generally considered more reliable than the leukocyte count The rate of sedimentation of the cells almost invariably increases during the acute phases of the infection with clin

ical improvement the rate decreases and returns to normal. In patients with carditis and cardiac failure normal values may be obtained, but as failure disappears the sedimentation of the cells increases.

The determination of C reactive protein content of the blood is a useful procedure in judging rheumatic activity. Since this protein also appears in the blood during the course of acute bacterial infections, the reaction must not be considered specific. Culture of the tonsils and oropharynx may show beta streptococci of Lancefield group A, but failure to isolate these organisms even early in the course of the disease is not unusual. Of significance is the finding of a high antistreptolysin titer which falls during the convalescent period. Antistreptolysin titers of 200 or more indicate a recent infection by group A streptococci; they are not diagnostic of rheumatic fever. Early in the course of rheumatic fever titers of less than 100 are rare.

Diagnosis. There is no laboratory test available that establishes the diagnosis of acute rheumatic fever. *Polyarthritis, carditis, chorea, subcutaneous nodules, erythema marginatum* and *recurrent attacks* characterize the disease. According to Jones the diagnosis of rheumatic fever becomes established when two or more of the above manifestations coexist. It should be emphasized that rheumatic fever undoubtedly occurs in the absence of these conditions, but only by long observation is it usually possible to make certain of the diagnosis.

Rheumatic fever must be differentiated from other forms of acute arthritis. Under the age of twenty *gonococcal arthritis* may be confused with rheumatic fever (see p 875).

Rheumatoid arthritis, although relatively rare in children, is generally polyarticular in its manifestations, so that it is commonly confused with acute rheumatic fever (see p 1718). Temporomandibular joint involvement is rare in rheumatic fever and common in rheumatoid arthritis. The development of deformities or ankylosis clearly indicates rheumatoid arthritis.

Septic or *purulent arthritis* is recognized readily in most instances, and cultures of the blood and joint fluid establish the correct diagnosis. *Tuberculous arthritis* is usually monoarticular in distribution and subacute in its course. Some cases of acute *disseminated lupus erythematosus* may be difficult to distinguish from acute rheumatic fever. The former disease almost invariably occurs in females and is associated with leukopenia, hematuria and in most instances a rash over the face (see p 1700).

In the adult, and especially in the male, *gout* must be considered. The occurrence of tophi, podagra and an increased uric acid content of the blood, as well as the appearance of erosions of the bone in the roentgenograms, serve to differentiate gout from rheumatic fever.

The administration of salicylic acid compounds is often helpful in differential diagnosis. In rheumatic fever these drugs produce rather marked symptomatic relief; the temperature decreases and the pulse slows.

In patients with fever and valvular heart disease *subacute bacterial endocarditis* may mimic rheumatic fever. Here the presence of petechiae, enlarged spleen, hematuria or a positive culture of the blood assist in establishing the diagnosis.

Course and Prognosis. Approximately 4 per cent of hospitalized patients die during their initial attack of rheumatic fever, and in every instance death is due to active carditis. The course of the acute illness is extremely variable and prognosis should be guarded. In a few patients a normal status is apparent within 1 week, but the majority require 4 to 6 weeks before the clinical and laboratory signs of activity disappear. In the past there was an appreciable number of patients who continued to exhibit signs of rheumatic fever, either progressive or cyclic in nature. Today such a course is rarely observed, presumably because of better therapy rather than because of a fundamental change in the character of the rheumatic process.

The most important feature of rheumatic fever is carditis. If the patient is going to manifest disease of the heart, signs are readily detected early in the acute illness. Patients who subsequently develop chronic valvular heart disease usually exhibit murmurs during the acute illness. Although there is some correlation between the severity of acute carditis and chronic valvular deformities, it is difficult to make a prognosis until the patient has been observed for many months. The occurrence of repeated attacks of rheumatic fever alters the prognosis considerably. Repeated attacks usually result in serious cardiac injury.

Although death in the child is usually due to active carditis, in the adult mechanical failure of the heart results from marked valvular deformities. The adult patient succumbs to heart failure with auricular fibrillation, embolic episodes or bacterial endocarditis. The latter complication develops most frequently in patients who do not exhibit signs of failure during the acute illness. In all patients showing signs of cardiac failure active rheumatic fever should be suspected.

Treatment. During an attack of acute rheumatic fever attention is directed toward providing nursing care, a good diet, adequate fluid intake and rest in bed. Most physicians believe that *bed rest* is an important feature of treatment, and it undoubtedly is in patients with severe carditis. Absolute bed rest is difficult to maintain during therapy because the drugs employed relieve all symptoms in the majority of instances. It is common practice to require bed rest until clinical signs of activity have

disappeared The pulse rate leukocyte count sedimentation rate and C reactive protein are employed as an index of activity of the disease Some restriction of physical exertion is advised until these indices return to normal values

Patients with severe arthritis or substernal pain may require codeine or morphine for immediate relief The development of cardiac failure is an indication for digitalis therapy although occasionally such treatment is not followed by rapid improvement

Chorea requires special attention The patient should be placed in bed in a quiet room Precautions must be instituted so that the patient does not injure himself Feeding if difficult requires an understanding nurse Sedation usually phenobarbital should be administered in sufficient quantities to supply required rest

Once the diagnosis of rheumatic fever is established all patients should receive a course of penicillin therapy in amounts necessary to eliminate the group A streptococcus Penicillin is not withheld in patients whose oropharyngeal cultures are negative since studies have shown that the streptococci may be in inaccessible areas At present 500 000 units of penicillin is administered intramuscularly every 4 hours for 2 weeks This is followed by a single injection of 1 200 000 units of benzathine penicillin An alternative method is the injection of 600 000 units of procaine penicillin twice daily for 2 weeks to be followed by an injection of benzathine penicillin

Symptomatic therapy of acute rheumatic fever is accomplished by the use of salicylates or one of the adrenal steroid hormones All these compounds exert a favorable effect on the arthritis and the constitutional symptoms but only cortisone and hydrocortisone have been shown to alter the evolution of valvular heart disease It must be emphasized that the effect of cortisone on carditis is not marked but if therapy is instituted very early in the course of the disease a favorable effect can be demonstrated If the illness is of over 2 weeks duration at the time treatment is instituted the value of hormone therapy is doubtful Considerable more data are required before final evaluation of the role of the hormones in treatment of rheumatic fever can be determined

Sodium salicylate or acetylsalicylic acid rapidly relieves such symptoms as joint pain tachycardia and anorexia Unfortunately symptoms of salicylism appear early so that careful adjustments are necessary to obtain maximum relief of symptoms Small doses of these compounds given at frequent intervals are preferable to large doses In the adult 8 to 10 Gm during a 24 hr period may be required for maximal effect Enteric coated pills may be employed when there is intolerance Aminopyrine has been substituted for salicylates but because of its tendency to produce agranulocytosis it is not widely employed If used doses of 0 5 Gm may be given every 4 hr The leukocyte count should be followed in all patients receiving this drug

Hormone therapy is advised for all patients whose illness is of less than 2 weeks duration Corticotropin cortisone hydrocortisone and prednisone have been employed but most experience has been reported with cortisone and hydrocortisone Hydrocortisone is given in divided doses of 300 to 600 mg daily The dose is gradually reduced unless signs of activity are manifest Treatment is continued in general until there is no further improvement of the cardiac murmurs The usual course of treatment is 4 to 8 weeks After the drug is discontinued signs of activity may recur the so called "rebound phenomenon" If the rebound is not accompanied by severe symptoms it is not necessary to resume therapy Prednisone may be substituted for cortisone and has the advantage that it entails less risk of fluid retention

In all patients with active rheumatic fever and especially those receiving hormone therapy continuous prophylactic administration of sulfadiazine or penicillin should be instituted immediately after the first 2 weeks of therapy The physician should be careful in the management of each patient to make certain that a psychologically crippled individual is not produced Likewise the importance of continuous observation and prevention of recurrences should be stressed

Acute Glomerulonephritis

Most of the knowledge of acute glomerulonephritis has accumulated from study of hospitalized patients and of necessity has been derived only from individuals with symptoms Observation of patients infected with nephritogenic streptococci reveals that the spectrum of nephritis is broad many individuals exhibit signs of the disease without associated symptoms Since relatively few patients have been observed from the streptococcal infection throughout life knowledge concerning the evolution of the renal lesion is limited With the introduction of needle biopsy of the kidney the relationship of chronic nephritis to acute nephritis can be expected to be clarified in the future

The symptoms and signs of acute nephritis can be produced by a number of stimuli in addition to infection by nephritogenic streptococci Pneumococcal and other bacterial infections may be associated with hematuria and albuminuria with or without edema and hypertension Some of these illnesses are undoubtedly acute exacerbations of chronic nephritis whereas others may have resulted from infection with group A streptococci but the techniques for isolating the organism were not ade

quate In addition signs of nephritis may be produced by bee stings chemical poisons and bacteremia However most acute glomerulonephritis is caused by a few serologic types of group A streptococci

Clinical Manifestations An acute respiratory illness is an integral feature of acute glomerulonephritis Approximately 80 per cent of patients infected with group A streptococci experience clinical manifestations Since such infections are not always associated with a recognizable illness it is not surprising that a few patients exhibit no symptoms In addition in children the symptoms referable to the respiratory system may be overshadowed by infection of the skin Eczema or small abrasions may become infected by nephritogenic streptococci and may dominate the initial clinical picture presented by the patient In such instances bacteriologic studies of the oropharynx usually reveal group A streptococci

Symptoms of nephritis may develop during the acute respiratory illness but commonly they develop 10 days later Thus the symptoms of the acute respiratory illness subside or disappear completely prior to the onset of the nonsuppurative complication Occasionally the latent period may be as long as 4 weeks

As already stated most knowledge of acute glomerulonephritis is derived from the study of hospitalized patients In this population the manifestations are of such a nature that they are considered to be serious by the patient as well as by the physician Actually nephritis frequently produces few or no symptoms the only sign being an increased excretion of red blood cells Symptoms if present include vague lumbar soreness transient pain in the groins or abdomen anorexia and general malaise

In patients seeking medical care because of the development of nonsuppurative disease of the kidney *the symptoms include puffiness of the eyes* gross hematuria and headache Less commonly the initial symptom may be pain in the lumbar area severe pain in the groin or deep in the abdomen convulsions pulmonary edema and coma Any combination of the above symptoms may be associated with anorexia vomiting oliguria or anuria and nitrogen retention

Edema is one of the most common manifestations of acute nephritis Characteristically the parents observe that the face is swollen especially around the eyes The edema is most apparent upon arising in the morning Edema fluid frequently becomes manifest in the lower extremities over the sacrum or in the body cavities The exact mechanism involved in production of edema in acute nephritis is unknown but presumably it is due to sodium retention Other factors which may play a role are capillary damage and congestive heart failure Since the edema fluid exhibits a low protein content it is difficult to explain the accumulation of fluid by capillary damage

Some degree of *hematuria* is observed in all patients and the diagnosis of nephritis should not be made in its absence Individuals infected with group A streptococci exhibit an increased number of red cells in the urine during the febrile period If the organism is nephritogenic the "febrile hematuria" is even more marked 20 per cent may show over 20 cells per cubic millimeter in the uncentrifuged specimen This initial hematuria disappears only to recur in a few days in those patients who develop acute glomerulonephritis There is some evidence that "febrile hematuria" is especially likely to occur in patients who subsequently develop nephritis

Gross hematuria especially when it occurs in the male may be the presenting symptom Somewhat less than half the patients observe brown urine which lasts only a few days Since the blood must travel a long distance through the nephrons the color of the urine differs from that observed in hemorrhage from the bladder The red cells have been exposed to an acid environment which produces the brown or coffee grounds appearance Microscopic hematuria may persist for weeks and occasionally for months There is poor correlation between the severity of nephritis and the degree of hematuria

One of the characteristic signs of acute nephritis is *hypertension* The blood pressure tends to be extremely labile especially during the initial phase of the disease Patients with a normal pressure have been observed to develop marked hypertension edema cardiac dilatation and signs of failure immediately following stimuli such as an alcohol sponge bath administered as treatment for fever Observations such as this suggest that arteriolar *spasm is responsible for elevated pressures* Hypertension if it develops is likely to become manifest within a week or so of onset

Convulsions visual disturbances and coma appear to be related to the general vascular instability Sudden elevation of pressure is associated with severe headache nausea vomiting and rarely results in actual rupture of a cerebral vessel Generalized convulsions which occur mainly in young children may be the first or major symptom Blurring of vision or even amaurosis may be experienced Examination shows papilledema rarely hemorrhages into the retina and constriction of the arteries

The patient who develops hypertension is especially susceptible to vascular congestion The symptoms of congestive failure may develop rapidly *reaching a critical stage within a few hours Death*

in the early phase of the disease is commonly due to congestive failure The symptoms vary considerably from moderate dyspnea to frank signs of pulmonary edema and acute congestion with enlargement of the liver rapidly accumulating edema and elevated venous pressure

Laboratory Findings The function of the kidney is altered in many patients but specific data are meager concerning function in the patient without edema or hypertension and in the very early stages of poststreptococcal nephritis The ability to excrete water may be normal or impaired In the initial phases the ability to concentrate is usually maintained During convalescence the specific gravity may remain relatively fixed near 1 010 for several weeks or months The urea clearance may be depressed and the excretion of phenolsulfonphthalein decreased The discrete measurements show that the glomerular filtration rate is reduced in most cases renal plasma flow is normal or slightly depressed and there is a low filtration fraction There is evidence of some dysfunction of the tubular cells In patients with small urinary volumes and edema there may be azotemia

As stated under Clinical Manifestations *hematuria* of varying degrees is a constant finding in acute glomerulonephritis Microscopic examination shows red cells of normal size but in addition there are many small distorted erythrocytes and red cell stroma Identification of the distorted cells and stroma can best be accomplished in a fresh uncentrifuged specimen Bleeding from other areas of the urinary tract is not associated with abnormal cells or stroma For the proper interpretation of hematuria as well as for the long term management of the patient quantitative measurements of red cell excretion are required In the past these values have been expressed on the basis of 24 hr excretions by the method of Addis A much simpler technique is the enumeration of cells in the hemocytometer employing a fresh morning specimen which has not been stored in the icebox The cells are not sedimented prior to counting since this procedure ruptures many abnormal cells and makes the cell membranes stick together in a homogeneous mass Normal individuals excrete less than 10 red cells per cubic millimeter Patients with acute nephritis usually excrete over 100 cells although in very mild attacks or during the convalescent stages the number of cells may vary between 10 and 100 Normal individuals especially females will occasionally exhibit counts between 10 and 100 but subsequent examinations will show normal counts Some increase in cells occurs in urine containing sperm and such urine should not be considered abnormal Likewise during acute infections heart failure and infections of the urinary tract an increased number of cells is observed The presence of bacteria leukocytes and epithelial cells should be recorded The number of leukocytes is usually increased in acute nephritis If abnormal numbers of erythrocytes are observed an aliquot of urine is centrifuged and the sediment examined for casts The presence of red cell casts indicates bleeding from the glomerulus

Proteinuria is common and is always present in patients exhibiting edema or hypertension In contrast to common belief protein may be absent or present in very small quantities in patients without hypertension or edema In patients exhibiting marked degrees of proteinuria without signs of edema the illness most likely represents an acute exacerbation of chronic nephritis or some other form of renal disease

In each patient a careful search for evidence of a streptococcal infection should be made Several cultures of the throat should be obtained before institution of chemotherapy The culture is inoculated on the surface and subsurface of sheep blood agar since nephritogenic organisms frequently fail to produce typical hemolytic zones by other techniques Specimens from all members of the immediate family and other household contacts should be cultured to obtain evidence of infection in this group Those with positive cultures should be followed for urinary abnormalities Blood for antistreptolysin determinations should be taken especially in those who exhibit a negative throat culture A very high titer or a rising titer indicates a recent streptococcal infection

In acute nephritis during the active phase of the disease the sedimentation rate is increased and there may be anemia The total serum protein may be depressed slightly

Diagnosis The patient who develops hematuria edema and transient hypertension following a respiratory illness characterized by soreness on swallowing presents no difficulty in diagnosis Since hematuria is a necessary component of acute streptococcal glomerulonephritis it is necessary to consider other causes of bloody urine Bleeding from kidney or bladder tumors calculi or trauma is usually bright red and is not associated with edema or hypertension History roentgenograms of the urinary tract and microscopic examination of the urine are sufficient to establish these diagnoses Hematuria is also observed in patients with lupus erythematosis periarteritis nodosa endocarditis and bacteremia but here again other features of the history and presenting physical signs serve to differentiate the disease from diffuse glomerulonephritis

Bacterial infections of the urinary tract including tuberculosis commonly cause some hematuria but bacteriologic studies and the presence of large numbers of leukocytes indicate the correct diagnosis

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The patient who develops hypertension is especially susceptible to vascular congestion The symptoms of congestive failure may develop rapidly reaching a critical stage within a few hours Death

During the first 2 weeks of illness and especially in patients exhibiting edema hypertension or oliguria the nutrition fluid and electrolyte intake should be carefully controlled The value of a low protein diet has not been established in man but in experimental nephritis in rats a high protein diet produces an adverse effect Another reason to limit the protein is the high potassium content Fluid should never be forced and should be limited in patients showing edema or hypertension Potassium intake should also be limited

In the treatment of *circulatory congestion* digitalis is of little value Diuretics are seldom employed but phlebotomy of 400 ml may prove beneficial

Hypertension and convulsions are difficult to control As mentioned above bed rest and limitation of sodium intake are important preventive measures In severe hypertension protoveratrine is administered in doses of 0 25 mg every 6 hr If convulsions are frequent 250 ml of a 2 per cent solution of magnesium sulfate is administered intravenously

Prevention of Rheumatic Fever and Nephritis

Both initial and recurrent attacks of rheumatic fever and nephritis can be prevented Prompt and adequate treatment of group A streptococcal infections will prevent both complications and continuous prophylaxis will greatly reduce the number of recurrences in patients who have already had an attack of rheumatic fever

It is now well established that therapy of streptococcal infections which eliminates the infecting organism will prevent initial attacks of rheumatic fever and nephritis If the organism is not eliminated the attack rate of rheumatic fever is not altered The preferred method of therapy is either a single injection of 900 000 units of benzathine penicillin or 200 000 to 250 000 units of penicillin V four times daily for at least 10 to 14 days If the patient is sensitive to penicillin, erythromycin or the tetracyclines are given in full doses for 10 to 14 days Treatment should be instituted promptly especially if acute nephritis is to be prevented Therapy instituted after symptoms of the acute respiratory illness have subsided will still prevent the onset of rheumatic symptoms Since the sulfonamide drugs are bacteriostatic they should never be employed for the treatment of streptococcal infections

Once rheumatic fever develops penicillin should be administered in full therapeutic doses in order to eliminate the streptococcus This therapy is advised under the assumption that the organism may be contributing to the rheumatic process Eradication of the streptococcus should alter the disease in a favorable fashion but evidence establishing the efficacy of such therapy is not available

From 20 to 80 per cent of streptococcal infections which occur in individuals who have had an initial attack of rheumatic fever are followed by recurrences Since many streptococcal infections produce no symptoms it is not possible to rely on treatment of the infection for the prevention of recurrences For this reason patients with rheumatic fever or established rheumatic heart disease should be protected continuously against streptococcal disease This is best accomplished by the intramuscular administration of 1 200 000 units of benzathine penicillin once each month Oral prophylaxis which depends upon full cooperation of the patient is obtained by the daily administration of 0 5 to 1 0 Gm sulfadiazine Penicillin may be employed but medication must be given twice daily in doses of 250 000 units Prophylaxis is maintained throughout the year Except in individuals who show no evidence of valvular heart disease or in a few patients in whom the risk of contracting a streptococcal infection is considered negligible prophylaxis is continued indefinitely

Patients with rheumatic valvular heart disease subjected to surgical procedures especially tooth extractions should receive penicillin as a prophylactic measure before and several days after the operation It is believed that such treatment will prevent the development of subacute bacterial endocarditis

The problem presented by the patient with acute nephritis differs from that posed by the patient with rheumatic fever The appearance of a case of acute nephritis in the hospital or physician s office indicates that a nephritogenic type of streptococcus is circulating in the population Since the attack rate of nephritis may be very high following infection with these organisms the physician has a duty to the public to eliminate the streptococcus from both the patient and all contacts Spread of streptococci is especially likely to occur in the home and school Therefore cultures of the throat should be obtained from contacts in these two areas Individuals with positive cultures should receive therapy in a form sufficient to eliminate the organism In addition the urine should be examined microscopically for unapparent cases of nephritis will be found in persons found to have a positive culture

Once the patient has *recovered* from the acute phase of nephritis it is not necessary to institute prophylaxis against streptococcal *infection* Recurrences are rare if they occur at all The most likely explanation for this fact is that the patient acquires lasting immunity against the infecting type of streptococcus and statistically has little chance to be infected with another type possessing nephritogenic qualities It is also possible that the substance responsible for nephritis is antigenic thus antibody

The diagnosis of acute nephritis is frequently not considered in patients who exhibit only pain in the groin or abdomen or gross hematuria Such patients are thought to have acute appendicitis or small renal calculi but careful examination of the urine will show red cell casts which establish the proper cause of the symptoms

The most difficult diagnostic problem is the recognition of exacerbations of chronic glomerulonephritis Here the presenting symptoms may be identical to those exhibited by patients with acute nephritis caused by nephritogenic streptococci Some clue is afforded by the absence of a preceding streptococcal illness the sudden onset of symptoms without a latent period and the finding of a high degree of proteinuria Exacerbations of chronic nephritis are characterized by an insidious onset marked proteinuria and persistent edema Any infection may precipitate the illness Since streptococcal infections are common it is to be expected that individuals with chronic nephritis will acquire these infections The identification of the serologic type of streptococcus becomes important in these patients since the isolation of a type not possessing *nephritogenic qualities may indicate the proper* diagnosis

Patients presenting a nephrotic syndrome may show hematuria and hypertension Here chemical studies of the blood are of assistance The findings of low serum protein and high cholesterol indicate chronic renal disease

Finally increased excretion of red cells is observed in many patients with acute infections In the majority of these the hematuria along with slight albuminuria disappears soon after the temperature returns to normal In contrast following infection with nephritogenic streptococci the hematuria returns and persists for several days or weeks During this second episode of hematuria proteinuria is not a characteristic feature It seems likely that such cases represent a mild form of acute nephritis

Course and Prognosis The course of acute nephritis is extremely variable In hospitalized cases 3 to 5 per cent die In most instances death occurs in patients presenting a syndrome resembling heart failure Since these patients exhibit retention of water oliguria and hypertension it is difficult to determine the pathogenesis of the apparent heart failure Occasionally death is due to uremia convulsive seizures infection or rupture of a cerebral vessel

Two different courses of illness are observed in patients who do not die during the acute phase In one complete recovery is the rule and only rarely do signs of chronic nephritis develop whereas in the other group the majority develops chronic progressive renal disease There is reason to believe that acute nephritis caused by nephritogenic streptococci does not lead to chronic nephritis Patients who give a classical history of a preceding respiratory infection or develop nephritis following scarlet fever rarely develop chronic nephritis (Ellis type I) These patients usually seek medical attention within a few days after the onset of symptoms of nephritis In contrast the patient who exhibits an insidious onset of nephritic symptoms gives no evidence of a recent streptococcal infection shows large amounts of protein in the urine or develops hematuria without a latent period is especially likely to exhibit chronic progressive renal disease The illnesses in this group of patients (Ellis type II) may represent exacerbations of chronic nephritis Recent studies show that the serum from these patients contains no antibody against nephritogenic organisms whereas such antibodies can be demonstrated in many patients who have recovered following an attack of type I nephritis

The clinical signs of nephritis observed following infection with nephritogenic streptococci last only a few weeks Edema hypertension and gross hematuria disappear within a few days or weeks *Persistence of these signs for more than 2 months* is a bad prognostic sign and may indicate chronic renal disease Abnormal numbers of red cells and moderate proteinuria may persist for months in a few patients Individuals who recover from acute nephritis rarely experience another attack

Treatment *Bed rest* is necessary in the early phases of an attack of acute nephritis During the first week or two physical exertion or sudden stimuli such as an alcohol rub or news of death in the family may precipitate severe hypertension pulmonary edema convulsions cerebral hemorrhage or coma If possible the patient should be placed in a single room mild sedation should be administered few or no visitors should be permitted and the number of examinations and procedures should be kept to a minimum Bed rest should be enforced until the blood pressure has become stabilized and signs of edema have disappeared Restricted activity is advisable until the sedimentation rate is normal and the number of red cells excreted is not altered significantly by exercise There is no evidence indicating that activity is harmful to the patient who continues to excrete red cells in moderate numbers during the convalescent period

Patients infected with nephritogenic streptococci who subsequently develop nephritis are especially likely to exhibit abnormal degrees of hematuria during the acute respiratory infection Since this may indicate that some product of these organisms damages the glomerulus directly the organism should be eliminated This is best accomplished by the administration of procaine penicillin in doses of 600 000 units twice daily for 2 weeks

of infection Penicillin and streptomycin in combination exert a synergistic effect against enterococci and are indicated in the treatment of bacterial endocarditis caused by them or in other enterococcal infections not responding to tetracyclines In cases of enterococcal endocarditis a regimen of at least 10 million units of penicillin and 1 Gm of streptomycin daily for 6 weeks is indicated If clinical improvement is not evident within a short time the amount of penicillin should be increased Although 2 weeks of intensive combined chemotherapy has been shown to be adequate in most cases of *Streptococcus viridans* endocarditis at least 6 weeks of therapy is essential in those caused by the enterococci

Streptococcus viridans No "C" polysaccharide which would permit etiologic classification has been demonstrated in members of this heterogeneous group and biochemical reactions have been used to characterize the several subtypes Of those important to man the majority produce greening on blood agar plates although a few strains are nonhemolytic These bacteria are members of the normal throat and mouth flora and only rarely incite disease They frequently invade the blood stream following dental manipulation and indeed following mastication where dental hygiene is poor Their chief pathogenicity is displayed in patients with acquired or congenital vascular lesions where they become implanted following bacteremia and cause the majority of cases of bacterial endocarditis Some patients with atypical pneumonia develop agglutinins to a member of this group streptococcus "MG" The significance of this is not well understood these bacteria apparently are of no etiologic significance in such infections

Anaerobic Streptococcal Infections Anaerobic streptococci have been divided with difficulty into nine groups on the basis of fermentation reactions of five carbohydrates and five organic acids Most strains remain strictly anaerobic but some are able to grow without conditions of anaerobiosis on further subculture These organisms comprise part of the normal body flora being present in the nose and throat gums vagina and intestine They exist as commensals but in appropriate conditions can invade neighboring structures and incite disease Circumstances are most favorable for invasion and infection by anaerobic streptococci when necrotic tissue is present The lochia and necrotic cervical tissue of the parturient uterus devitalized tissue as in the postpneumonic lung or the necrotic tissue resulting from pulmonary infarction are examples The ensuing infection is characterized by further tissue destruction and by the production of foul smelling pus

Anaerobic streptococci occur in mixed culture in many instances often with bacteroides but can be the sole etiologic pathogen The spreading necrosis and foul pus of many pulmonary abscesses are usually attributable to these bacteria which frequently are part of a mixed flora In post partum infections caused solely by anaerobic streptococci the clinical syndromes run the gamut from putrid endometritis with low grade fever foul lochial discharge and a soft tender subinvoluted uterus to septic pelvic thrombophlebitis with resulting metastatic abscess formation throughout the body particularly in the lungs

The rapid accumulation of air in anaerobic streptococcal empyema results in part from gas produced by fermentation of carbohydrates by the bacteria and from the frequent occurrence of bronchopleural fistulas A syndrome simulating clostridial gas gangrene may result from infections of devitalized muscles by gas producing anaerobic streptococci Although the spreading crepitation resembles that of clostridial infection the overwhelming toxemia of the latter is absent

Anaerobic streptococci assume a pathogenic role in some infected human bites Infections of the paranasal sinuses or mastoid cells by these bacteria produce the same picture as infections of these structures by other bacteria On occasion they may extend into adjacent cranial bones with resulting osteomyelitis Direct extension into the brain may occur

Treatment Penicillin remains the drug of choice in anaerobic streptococcal infections Large doses of this antibiotic are indicated and in some infections the tetracycline antibiotics may be effective All attempts should be made to evacuate collections of pus penicillin should be instilled locally into the infections of serous cavities such as the pleura

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against the hypothetical nephritogenic toxin might afford a protective mechanism

Individuals who present signs of chronic glomerulonephritis may suffer exacerbations following bacterial infections including those caused by any type of group A streptococcus In these patients the monthly injection of 1 200 000 units of benzathine penicillin may be advisable

Tonsillectomy has been considered effective in preventing rheumatic fever and nephritis There is no evidence to substantiate this suggestion On the contrary the risk of developing rheumatic fever or nephritis is increased because after tonsillectomy the physician is less likely to make the correct diagnosis and therefore less likely to prescribe adequate treatment

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114 OTHER STREPTOCOCCAL INFECTIONS

Max Michael Jr

In addition to the group A beta hemolytic streptococci many other streptococci possess a polysaccharide "C" antigen which permits classification into twelve groups (A N) Those of group A however are by far the most common pathogens All these Lancefield types can produce disease in man but with the exception of group D (enterococci) they are rarely incriminated Groups B and C are pathogenic for cattle and horses and on rare occasions may cause sore throat mastoiditis and other purulent infections in man Groups F and G may cause occasional cases of tonsillitis in human beings

Enterococci (*Streptococcus faecalis*) These organisms can be alpha hemolytic beta hemolytic or nonhemolytic The alpha hemolytic strains are confused with *Streptococcus viridans* but can be differentiated easily by their ability to reduce methylene blue and to grow in broth containing 6 5 per cent sodium chloride They are normal inhabitants of the female genital tract the gastrointestinal tract, and to a lesser extent the upper respiratory tract Invasion of contiguous structures or metastases by way of the blood stream are the modes of infection The enterococci are frequently present in the purulent peritoneal fluid following rupture of the appendix They may be the sole etiologic bacteria in infections of the paranasal sinuses mastoids meninges or gallbladder The most frequent site of enterococcal infection is the urinary tract where they are particularly likely to produce disease when obstructive forces such as calculi and prostatic hypertrophy are present They can be the sole etiologic agent in such infections but more often occur in combination with other bacteria particularly enteric organisms When they are isolated from the urine in pure culture their role as pathogens should be carefully determined by appropriate clinical and quantitative bacteriologic methods

Enterococci are responsible for approximately 10 per cent of cases of bacterial endocarditis Because of the therapeutic problems posed this is a particularly treacherous infection The clinical features of enterococcal endocarditis are in the main similar to those seen in *Streptococcus viridans* endocarditis In contradistinction to the latter however its metastatic lesions can become suppurative foci

Therapeutic Implications The antibiotic agents useful in group A beta hemolytic streptococcal infections are also indicated in infections of all other hemolytic streptococci except those of group D the enterococci Infections resulting from these organisms are susceptible to the tetracycline antibiotics the dosage being dependent upon the site

of infection Penicillin and streptomycin in combination exert a synergistic effect against enterococci and are indicated in the treatment of bacterial endocarditis caused by them or in other enterococcal infections not responding to tetracyclines In cases of enterococcal endocarditis a regimen of at least 10 million units of penicillin and 1 Gm of streptomycin daily for 6 weeks is indicated If clinical improvement is not evident within a short time the amount of penicillin should be increased Although 2 weeks of intensive combined chemotherapy has been shown to be adequate in most cases of *Streptococcus viridans* endocarditis at least 6 weeks of therapy is essential in those caused by the enterococci

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Section 3 Infections Due to Gram-negative Cocci

115 MENINGOCOCCAL INFECTIONS

Ivan L Bennett Jr

Definition The commonest infection produced by the meningococcus is a subclinical nasopharyngitis or upper respiratory carrier state In a relatively few individuals this is followed by invasion of the blood stream with involvement of the meninges and other sites or fulminating sepsis with rapid circulatory collapse and death

Etiology *Neisseria meningitidis* or *intracellularis* a gram negative coccus was shown to be the cause of cerebrospinal or "spotted" fever by Weichselbaum in 1887 In stained smears of exudates the organisms appear as biscuit shaped single cocci or *diplococci frequently within polymorphonuclear* cells closely resembling gonococci The meningococcus grows best when fresh inocula are incubated in carbon dioxide (candle jar) on media containing blood serum or ascitic fluid chocolate agar is frequently used Like other *Neisseria* the organism gives a positive oxidase test its colonies on solid medium turning purple when exposed to 1 per cent p aminodimethylanilidemonochloride The meningococcus is identified by its ability to ferment glucose and maltose The gonococcus ferments glucose only and nonpathogenic *Neisseria* (*N flava N sicca N catarrhalis*) ferment glucose maltose and sucrose or none of these sugars Meningococci have been classified into serologic types but these types are presently of interest only on epidemiologic grounds The clinical diseases produced by all serotypes are identical and all are susceptible to sulfonamides penicillin and several other antibiotics

Epidemiology Under ordinary circumstances 2 to 5 per cent of normal individuals harbor meningococci as part of the flora of the nasopharynx Studies such as that of Phair and Schoenbach in 1944 have shown that crowding during the winter months is associated with a rise in the asymptomatic carrier rate to as high as 40 to 90 per cent As the rate rises cases of systemic meningococcal infection appear but it is clear that fewer than 1 per cent of parasitized individuals develop serious illness The circumstances leading to spread of infection beyond the nasopharynx are unknown although several factors have been suggested (1) failure of nasopharyngeal infection to confer immunity—this is unlikely to play a role in that relatively few carriers are found to possess serum antibodies (2) in vivo development of invasive mutants (3) sudden introduction of a virulent strain into a population group (4) concomitant viral infection of the nose and throat—in army outbreaks recruits have been more susceptible to meningococcal infections during the seasoning period when upper respiratory infections are numerous Malnutrition trauma and debilitating disease seem to play no role Disseminated meningococcal infection is commoner in males and below the age of five years Mortality is greatest at the extremes of life Case to-case transmission is rarely demonstrated in epidemics and the frequency of asymptomatic carriers makes it obvious that strict isolation of clinical cases is unjustified Administration of sulfonamides or penicillin *to a patient results in rapid disappearance of* meningococci The prophylactic use of oral sulfadiazine in a dose of 1 to 2 Gm to a population reduces the carrier rate abruptly and can abort an epidemic in a school army post or other limited group

Pathogenesis Spread of organisms occurs by droplet infection the upper respiratory tract is the usual portal of infection although rare instances of isolated meningococcal conjunctivitis in which the eye was apparently a primary point of entry have been reported About 75 per cent of systemic infections are preceded by upper respiratory symptoms but the role of the meningococcus in these symptoms is difficult to assess Spread of infection beyond the nasopharynx is now known to occur almost exclusively via the blood stream Purulent meningitis the commonest metastatic complication is preceded by a bacteremia as are arthritis and rarer localizations such as ophthalmitis pneumonia pericarditis endocarditis empyema orchitis salpingitis and epididymitis Bursitis and tenosynovitis may complicate articular involvement which next to meningitis is the most frequent complication of meningococcemia occurring in about 3 per cent of cases

The meningococcus possesses an endotoxin similar to those of gram negative bacilli injection of these materials into experimental animals results in fever vascular damage shock and other toxic changes There is much to indicate that endotoxin may be responsible for the rapidly fatal course of fulminating meningococcemia with hemorrhagic skin lesions and circulatory collapse

Autopsy findings include widespread dermal and

visceral hemorrhage purulent meningitis basilar in distribution and in older cases extensive meningeal scarring and hydrocephalus Meningitis is often absent in cases of fatal meningococcemia the main findings consisting of large hemorrhages in the various organs and tissues Histologic examination reveals widespread thrombosis of small vessels and numerous areas of necrosis containing large numbers of meningococci The adrenal cortex may be grossly hemorrhagic and almost invariably contains microscopic lesions of severe and extensive degeneration

Clinical Manifestations The course of disseminated meningococcal infection is highly variable Clinically there are three main types *meningococcemia meningitis* and *fulminating sepsis*

Meningococcemia Invasion of the blood by meningococci may be followed almost immediately by meningitis or patients may be seen during the bacteremic stage Prodromal symptoms of upper respiratory irritation are followed by abrupt onset of fever often with a rigor myalgia headache nausea and particularly in children diarrhea Extreme tenderness of the soles of the feet without signs of local inflammation is highly suggestive of the disease many patients are thought in the beginning to have influenza or some other grippelike illness There is usually a polymorphonuclear leukocytosis of 12 000 to 40 000 per cubic millimeter The diagnosis is facilitated by the development of *skin lesions* in about three fourths of the cases The rash from which the disease derived the name "spotted fever" consists of petechiae of the skin and mucous membranes and typical bright pink nonpruritic tender macules or papules 2 to 10 mm in diameter over the extremities and trunk These lesions sometimes have hemorrhagic centers Hemorrhagic vesicles and larger cutaneous ecchymoses ("suggillations) sometimes occur Lesions may be few and careful search is essential in some cases the eruption is so profuse and rapid in onset that new lesions can be seen to appear within minutes

Splenomegaly is inconstant in the early stage conjunctivitis hemorrhages in the fundus oculi and arthritis are sometimes present but joint involvement is more frequent in the chronic stage of the disease

Chronic meningococcemia is characterized by periodic bouts of fever arthralgia or arthritis and recurrent cutaneous lesions The disease may continue for many months Splenomegaly is usually present and each recurrence is accompanied by polymorphonuclear leukocytosis Patients with this peculiar infection are usually asymptomatic between attacks The disorder is sometimes mistaken for malaria or allergic purpura The skin lesions can take any of the forms described above The majority of patients become asymptomatic after several weeks or months even without treatment a few finally develop endocarditis or meningitis

Meningitis In most patients the bacteremic stage is followed within a few hours or days by the onset of acute purulent meningitis with severe headache nuchal rigidity nausea vomiting disorientation and stupor Impairment of hearing occurs early and what appears to be lack of cooperation or inability to answer questions is sometimes attributable to this There is high fever respirations may be periodic and skin lesions are frequent Signs of meningeal irritation are prominent but papilledema is unusual

Fulminating Infections Meningococcemia can produce death within a few hours with the "Waterhouse-Friderichsen" syndrome of bacteremia massive skin hemorrhage and shock This triad can result from pneumococcal streptococcal or other infections but the meningococcus is the usual etiologic agent The complex is commoner in children below the age of five years

The onset is abrupt with fever and nonspecific discomfort until dermal petechiae appear and rapidly enlarge into areas of confluent purpura The blood pressure falls rapidly although the skin may remain warm to the touch Patients usually remain alert Ordinarily the infection leads to death within several hours Because bilateral adrenal hemorrhage is frequently present at autopsy and microscopic adrenal necrosis is invariable the role of acute adrenal insufficiency in this infection has been much argued The use of adrenal steroids is probably justified but therapeutic regimens have not been evaluated systematically In patients who recover oliguria may persist for 18 to 24 hr after blood pressure stabilizes and extensive sloughing of the skin lesions or loss of extremities from gangrene often prolongs convalescence Meningitis is not a usual feature

Rarely meningococcal infection may take an *encephalitic* course in which signs of meningeal infection are scanty but extensive cerebral involvement leads to stupor coma and death within a few days Circulatory collapse is not a prominent part of the picture except terminally Progressive signs of neurologic disturbance and papilledema are the outstanding manifestations

Laboratory Findings Polymorphonuclear leukocytosis is the rule In meningitis there is elevation of spinal fluid pressure and the fluid is cloudy (it may be clear early in the disease) containing from a few hundred to 40 000 polymorphonuclear cells per cubic millimeter Protein is elevated and the glucose content is low Albuminuria and microscopic hematuria are not infrequent and transient glycosuria is sometimes present

Specific diagnosis depends upon demonstration

of the meningococcus in smears or cultures of spinal fluid or material aspirated from skin lesions or joints Smears of body fluids stained with methylene blue are useful for detection of the organism *which is frequently contained in polymorphonuclear* leukocytes its gram staining reaction should be confirmed Confusion sometimes arises with *Hemophilus influenzae* which is gram negative and pleomorphic It is sometimes impossible to find meningocci in stained sediment of spinal fluid this is more likely to occur in this disease than in any other pyogenic infection of the meninges

So numerous are meningocci in the blood that it is not unusual to find them in smears of buffy coat material The skin lesions often contain many organisms also the skin around the lesion should be pinched up the lesion punctured and a drop of tissue fluid (not blood) smeared and stained

Material taken for culture should be inoculated immediately (preferably at the bedside) onto chocolate agar and incubated in a candle jar Meningococci can usually be cultured from the nasopharynx

Complications *Herpes labialis* is common in meningococcal infections particularly in meningitis Urinary retention is often a problem and patients must of course be guarded against the usual complications of coma including aspiration

Chronic hydrocephalus was formerly seen with considerable frequency it is now rare Transient *palsies of cranial nerves* occur and usually clear completely within 6 weeks *Blindness hemiplegia, myocarditis* with heart failure and *localized meningococcal infections* in other sites are all very rare *Deafness* of a degree detectable by audiometry is present in about 5 per cent of patients who recover from meningitis it is usually unilateral and severe impairment of hearing is now unusual

It is not unusual for patients to complain of fatigability headache dizziness and insomnia for many months after recovery It is believed that many of these symptoms result from injudicious psychologic management of patients during convalescence

Diagnosis The clinical diagnosis of meningococcal infection is easily made in patients with fever skin lesions and meningitis Diseases with which confusion can arise include other forms of meningitis bacterial and nonbacterial endocarditis the common exanthemas subarachnoid hemorrhage rickettsioses thrombocytopenic and other purpuras and drug eruptions Once the meningococcus is suspected as the etiologic agent the diagnosis can usually be established by demonstration of the organisms

Treatment When the clinical diagnosis of meningococcal infection has been made and specimens have been obtained for culture *specific antimicrobial* therapy should be instituted immediately Sulfonamides and penicillin are equally effective Sulfadiazine sulfamerazine and Gantrisin are excellent agents In patients with hypotension and oliguria *dosage should be reduced until urine flow is re*established Penicillin in a dosage of 1 2 to 2 4 million units per day in divided doses has the advantage of immediate bactericidal action in contrast to the 4 to 6 hr delay before sulfonamides begin to act for this reason penicillin is preferable in fulminating infections where a slight delay may be crucial Intrathecal administration of penicillin in a dose of 5 000 to 10 000 units is permissible but unnecessary The initial dose of penicillin should be given intravenously to patients with circulatory collapse Chloromycetin the tetracycline derivatives and other antibiotics are effective in meningococcal *infections but have not replaced sulfonamides* and penicillin as the drugs of choice There is no advantage to combining sulfonamides and penicillin although this is frequently done

Supportive therapy includes the usual precautions in patients who are delirious or stuporous sedation and relief of headache with Demerol which is less likely to aggravate urinary retention than are opiates Maintenance of fluid balance is particularly important if sulfonamides are given the majority of these patients are somewhat dehydrated when first seen because of vomiting and lack of intake There is nothing to be gained of course by overloading hypotensive patients with fluid during the oliguric phase of fulminating meningococcal infection It is extremely important to keep a careful *record of blood pressure and fluid balance* in all patients with meningococcal disease until a definite therapeutic response is evident

In patients with overwhelming meningococcemia and circulatory collapse prompt and vigorous antimicrobial therapy is the most important step Pressor amines may be given by intravenous infusion as may adrenal steroids the evidence for the effectiveness of these agents is incomplete and recovery has been reported without their use but the usual practice at present is to give them It is worth remembering that individuals with the Waterhouse Friderichsen syndrome are extremely susceptible to the local necrotizing action of pressor amines and extravasation into the tissues should be carefully avoided Large amounts of blood and plasma will not influence the hypotension and should not be given

The response of meningococcemia to treatment is dramatic defervescence usually occurs within 24 hr Patients with meningitis may continue to have some fever disorientation and meningeal signs for 2 to 5 days this should not lead to a change in chemotherapy Relapse is almost never

seen and although documented second attacks of meningococcal meningitis have been reported they are extremely rare

Prevention The frequency of carriers and the effectiveness of chemotherapy in rendering patients noninfectious makes the use of strict isolation technique for meningococcal infections both ineffectual and fallacious As has been mentioned the wholesale administration of 1 to 2 Gm sulfadiazine will reduce the carrier rate and abort an epidemic in closed populations When continued contacts with the general public are maintained however the effectiveness of this procedure is likely to be transient

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116 GONOCOCCAL INFECTIONS

Max Michael Jr

Definition Gonococcal infections comprise a group of syndromes with varied manifestations produced by a single etiologic agent the gonococcus (*Neisseria gonorrhoeae*) The organism has a predilection for the mucous membranes of the genital tract of both sexes but may incite disease processes in any region of the body particularly in synovial tissues and on serosal surfaces

Etiology The gonococcus is a gram negative oval coccus belonging to the genus *Neisseria* In stained films of purulent exudates the organisms appear predominantly in pairs the opposing surfaces being flattened or concave resulting in a characteristic biscuit or kidney bean–shaped appearance In cultures however there is considerable variation in size and shape of single cells and the flattening of opposing surfaces is seldom evident The gonococcus grows best on solid media enriched with protein such as blood plasma or ascitic fluid Moist atmosphere with 2 to 5 per cent carbon dioxide as attained in a candle jar" assists growth of the organism It is differentiated from other members of the genus *Neisseria* by its fermentation reactions on glucose maltose and sucrose and by agglutination reactions It is thought that two or more antigenic strains of the gonococcus exist Both nucleoprotein and polysaccharide substances have been identified in the cell but their relationship to more precise antigenic divisions has not been conclusively demonstrated The gonococcus contains an endotoxin No true exotoxin has been isolated

Epidemiology Gonococcal infection of the genital tract or gonorrhea is nearly always acquired by sexual exposure and is in fact the most common venereal disease It can be transmitted by sexual partners who have no symptoms of the infection It is difficult to estimate the total number of new cases of gonorrhea each year but it is estimated that approximately one million cases are acquired in the United States each year The lack of interest of the public and physicians alike concerning gonorrhea and the tendency to attach relatively minor significance to the infection have detracted from general appreciation of its true public health significance and its seriousness Although many cases of gonorrhea have relatively mild symptoms severe complications including a high degree of sterility may result from the disease

Gonococcal conjunctivitis of the newborn (ophthalmia neonatorum) is acquired in the infected birth canal but has been practically eliminated by routine instillation of silver compounds or penicillin into the eyes of the newborn Vulvovaginitis in young girls is now known to be nongonococcal in origin in many instances Most of the gonococcal vulvovaginitis can be traced to sexual contact infected linen and toilet seats play little or no role in the spread of this form of the disease

It has been demonstrated that individuals may harbor the gonococcus in their prostatic secretions for as long as 7 years without symptoms and hence serve as asymptomatic carriers

Pathogenesis In the majority of instances the gonococcus gains access to the body by way of the genital tract Less frequent sites of initial infections are the conjunctivas and rectal mucosa The type of mucosa found in a particular part of the genitourinary tract determines to a large extent the susceptibility of that tissue to gonococcal infection Stratified squamous epithelium which covers the external genitalia of both sexes extends for ap

proximately 2 cm into the male urethra and lines the adult female vagina is not susceptible to infection Columnar epithelium which lines the anterior urethra urethral glands prostatic ducts and prostate seminal vesicles vas deferens and epididymis in the male and Skene s Bartholin s urethral and cervical glands fallopian tubes and endocervix in the female furnishes fertile soil for growth of the *gonococcus* Transitional epithelium which lines the posterior urethra of the male the proximal half of the urethra in the female and the bladder of both sexes is susceptible to invasion by gonococci Within a short period of time however infection is spontaneously eradicated from surfaces lined with this type of epithelium unless they are being bathed in exudate coming from an active lesion Adequate drainage of infected glands and tissues formerly was regarded as essential for recovery before chemotherapeutic agents were available When no such drainage took place destruction of tissue and abscess formation with eventual fibrosis and cyst formation ensued Now however this does not appear to be such an important factor for recovery

From the genital lesion the infection may take any of the following courses (1) it may be completely eradicated either spontaneously or as the result of therapy (2) it may be spread locally by way of the lymphatics or by direct extension to involve other organs of the genitourinary tract (3) it may remain hidden in recesses of the genital mucosa not causing symptoms but producing the carrier state (4) it may invade the blood stream and set up metastatic lesions most important of which are arthritis and endocarditis

Since it is not possible to culture the gonococcus from many of the metastatic lesions of gonorrhea it has been suggested that these lesions represent an allergic response to antigenic fractions of the gonococcus or to tissues which have been altered antigenically in some fashion by the organism This however has not been definitely established

It is possible to produce acute gonococcal infection by reinfecting a person with chronic gonorrhea It is obvious that there is little if any immunity to gonorrhea but this point will need clarification when different strains of the gonococcus are better identified Attempts to evoke immunity to gonorrhea by vaccination have been unsuccessful

Manifestations ***Gonococcal Infection of Genital Tract*** After an incubation period of from 3 to 5 days gonorrhea in the *male* begins as an acute anterior urethritis manifested by purulent urethral discharge and burning on urination If not properly treated infection may spread to the posterior urethra with symptoms of frequency urgency and terminal hematuria Perineal discomfort may occur The prostate and seminal vesicles may also be involved and this may result in acute retention of urine and pain in the suprapubic region Acute seminal vesiculitis may cause high fever and pain that is referred to the suprapubic inguinal and sacral regions or to the hip on the involved side Puzzling syndromes of obscure fever and pain in the above mentioned regions are occasionally due to seminal vesiculitis Acute prostatitis may be accompanied by urinary retention elevation of temperature and the feeling of fullness in the rectum Rectal examination discloses the enlarged tender prostate gland More serious involvement is that of acute epididymitis which is accompanied by pain in the epididymis swelling and fever The resulting tissue destruction is responsible for many cases of sterility in males

Gonococcal urethritis is to be distinguished from nonspecific urethritis an entity in which the exudate is more watery and in which local symptoms of gonorrhea are absent there is furthermore no improvement following penicillin therapy Gram stain of the urethral exudate usually reveals gonococci when they are the etiologic agent more or less by definition these organisms are absent in nonspecific urethritis

The chronic stage of gonorrhea may be asymptomatic or may be manifested by a small amount of mucoid urethral discharge occurring in the morning (gleet) or by urgency and frequency of urination Chronic prostatitis in a small number of patients is due to previous gonococcal infection

Gonorrhea in the *female* also begins as an acute urethritis with frequency and burning on urination and purulent discharge Cervicitis may be present at the same time resulting in a profuse purulent vaginal discharge There may be local spread to Skene s or Bartholin s glands with resulting acute or chronic infection in these organs Spread from the cervix into the fallopian tubes produces the syndrome of acute salpingitis or pelvic inflammatory disease (P I D) This is manifested by severe pain in the lower abdomen with local spasm and tenderness high fever and leukocytosis vaginal discharge and painful urination Recurring bouts of salpingitis are frequent with involvement of the ovaries destruction of tissue formation of abscesses and palpable masses resulting in the frozen pelvis This is an important cause of sterility

Acute salpingitis must be differentiated chiefly from acute appendicitis and ectopic pregnancy though all causes of acute lower abdominal pain are to be considered A vaginal discharge caused by the gonococcus is to be differentiated from vaginal discharge caused by *Trichomonas vaginalis* cervical erosions and other local gynecologic disorders

Gonorrheal vaginitis in the *immature female* is not so common as formerly believed Many cases

previously considered to be gonococcal in origin are actually due to other microorganisms Because of the nature of the vaginal epithelium in the immature female the gonococcus finds susceptible tissue and causes purulent discharge redness of the vulva and introitus with accompanying malaise and some fever

Arthritis Gonococcal arthritis an acute inflammatory process is the commonest and most disabling metastatic complication of this disease and is more frequent in patients who have had multiple attacks of urethritis Although the incidence of gonorrhea continues at a high rate that of arthritis appears to be decreasing This probably results from the more prompt eradication of the organisms from the genital tract before metastatic or sensitized lesions can develop

PATHOGENESIS AND PATHOLOGY Two clinical syndromes are associated with gonococcal arthritis In approximately 25 per cent of the patients the gonococcus can be cultured from the synovial fluid in these patients the disease manifests itself as a specific infectious arthritis In the remaining cases the synovial fluid is sterile and some features of the disease follow certain of the patterns of rheumatoid arthritis In the former group the gonococcus reaches the joint by way of the blood stream and sets up a purulent infection In the latter group it is not certain whether the organisms reach the joint spaces and are rapidly destroyed or whether the arthritis is the result of sensitization of the synovial tissues by antigenic fractions of the gonococcus without actual bacterial invasion of the joint Pathologic material demonstrate certain differences in the two types In the infected type of arthritis there is an extensive inflammatory reaction of the synovial tissue with destruction of the superficial layer of synovial cells In the noninfected type of arthritis the synovial tissue proliferates thickens and is infiltrated by perivascular and subsynovial collections of lymphocytes plasma cells and macrophages Occasionally neutrophils are present The extensive exudative reaction is not seen The superficial synovial layer is not completely destroyed and in some phases may be seen to proliferate The findings in the former group are those of an acute bacterial infection while in the latter group they suggest the picture of a hypersensitivity reaction

The cell count of aspirated synovial fluid varies from 1 800 to 160 000 white cells per cubic millimeter in general being higher in those cases with infected fluids The fluid always has the characteristics of an exudate with predominance of polymorphonuclear leukocytes The sugar content of the synovial fluid is decreased but this is of little help in differentiating gonococcal from other forms of acute arthritis

Destruction of articular cartilage may be noted as early as 3 weeks after the onset of arthritis These changes are most apt to be seen in cases with infected synovial fluid Associated with the changes in the joint are periarticular inflammatory reactions which may later fibrose and contribute to ankylosis of the joints

CLINICAL FEATURES *Arthritis* most commonly occurs 1 to 3 weeks following genital involvement but at times the interval may be prolonged to months or years Factors predisposing to arthritis include pregnancy pelvic operations or instrumentation for ureteral stricture all of which may cause latent infection to flare up

The arthritis of gonococcal infection is polyarticular in about 85 per cent of the cases The joints most frequently involved are the knees ankles wrists metacarpophalangeals and shoulders in that order though any joint in the body may become infected The first signs noted are those of malaise and fleeting aches in several of the large joints Within 24 to 48 hr pain becomes more severe and more persistent After 3 or 4 days two or more joints become exceedingly painful and distended with fluid The overlying skin becomes red and the slightest motion causes severe pain Marked muscle spasm occurs around involved joints and is responsible for the rapid development of deformities A striking and rapid muscle atrophy adjacent to involved joints is a common feature

The course of gonococcal arthritis is exceedingly variable Some cases may be mild with transitory aches in the joints which clear rapidly in a few days without residua At the other extreme are cases that may progress to permanent bony ankylosis of the joints This termination occurs primarily in cases with infected fluids which are untreated and involves principally the smaller joints of the wrists and hands

In a small group of patients a picture resembling rheumatoid arthritis occurs as a sequel to gonococcal infection It is not certain whether this represents gonococcal arthritis evolving into the rheumatoid picture or whether it is simply rheumatoid arthritis precipitated by the gonococcal infection Rheumatoid nodules are not seen

The systemic response varies considerably Fever between 100 and 102 F is usually present though extremes from normal to 105 F may be observed Chills are infrequent but may be seen particularly in patients with monarticular involvement It is in this group that bacteria are cultured from the joint fluid

A characteristic feature is tenosynovitis This appears in approximately 40 per cent of the patients and occurs most frequently about the wrists dorsum of hands and feet and around the internal and external malleoli Tenosynovitis may be confused with arthritis unless careful evaluation of

joint mobility is made Occasionally tenosynovitis may be the only sign of the gonococcal infection The occurrence of tendon sheath involvement is more frequent in gonococcal arthritis than in any other type of arthritis and may be a valuable diag nostic sign Acute bursitis is sometimes noted

Catarrhal conjunctivitis occurs in approximately 15 per cent of cases and may also be helpful in diagnosis Organisms have not been cultured from these lesions The conjunctivitis may precede ac company or follow the arthritis A less frequent but more serious ophthalmic manifestation is irido cyclitis which may lead to blindness

Keratodermia blennorrhagica an interesting but rare form of cutaneous lesion may accompany gonococcal arthritis This lesion occurs most fre quently on the plantar surface of the feet and con sists of thickening of the skin some of which may become necrotic There is sharp demarcation be tween involved areas and the surrounding skin

The diagnosis of gonococcal arthritis can be simple particularly in patients with acute poly arthritis following a urethral discharge in which the gonococcus has been demonstrated Associated conjunctivitis and tenosynovitis are characteristic and may be of help in diagnosis

In the differential diagnosis rheumatic fever rheumatoid arthritis in the acute stage and Reiter s disease offer the greatest problems Gout may also imitate this disease The use of salicylates may be of some diagnostic aid since gonococcal arthritis usually does not respond as dramatically as does rheumatic fever The most confusing syndrome to be differentiated is Reiter s disease which is char acterized by urethritis arthritis and conjunctivitis (see p 1154) It is only by correlation of careful clinical observations of the patient the course of the illness response to chemotherapy precise bac teriologic studies and the judicious interpretation of the gonococcal complement fixation test that gonococcal arthritis may be differentiated from the conditions mentioned above In cases of gonococcal arthritis in which response to penicillin is relatively prompt this therapeutic test serves as an important diagnostic aid

Perihepatitis An infrequent complication of gon orrhea in the female is the occurrence of upper abdominal peritonitis or perihepatitis Gonococci have not been cultured directly from the lesions but the organisms are assumed to reach this area by direct extension over the posterior peritoneal gutter When the lesions heal characteristic "violin string adhesions are formed The symptoms of perihepatitis which may occur as long as 5 years after the initial attack of gonorrhea consist of a sudden onset of sharp pain in the upper abdomen with a moderate elevation of temperature The pain may be referred to the shoulder and is exaggerated by coughing or deep breathing A friction rub is occasionally heard over the liver and infrequently small pleural effusions develop on the side of the lesion If untreated perihepatitis subsides gradually over a period of 1 to 4 weeks No incapacitating sequelae are known

Gonococcal Endocarditis The gonococcus is a rare cause of bacterial endocarditis The clinical picture is similar to that of acute endocarditis caused by other microorganisms Involvement of the valves of the right side of the heart is not in frequent A double daily temperature elevation is occasionally seen and may be of some assistance in diagnosis Arthritis frequently coexists Peripheral emboli occur as in other forms of endocarditis Another characteristic feature is involvement of normal heart valves in 90 per cent of the cases

Bacteremia Transient invasion of the blood stream by the gonococcus probably occurs fre quently but is accompanied by no symptoms other than chill in a few patients with gonococcal ar thritis Constant invasion of the blood stream how ever produces a bacteremia characterized by chills fever polyarthritis prostration and a macular erup tion of the trunk and extremities The rash rapidly becomes vesicular pustular and hemorrhagic This rare complication of gonorrhea is more common in females Until chemotherapeutic agents were avail able recovery occurred in from 3 weeks to 3 months

The dissemination of the gonococcus by way of the blood stream accounts for some of the rare manifestations of the disease such as meningitis periostitis suppurative myositis perichondritis liver abscesses and myelitis It is apparent that few if any regions or organs of the body are free from attack by the gonococcus

Laboratory Diagnosis The chief laboratory meth ods of diagnosis depend upon the demonstration of the organism by smear and by confirmatory cultures In smears of purulent exudate stained by the Gram method the organisms are seen as the characteristic gram negative biscuit shaped diplococci often located within the cytoplasm of polymorphonuclear leukocytes This is sufficient evidence for a positive diagnosis but failure to demonstrate the organism does not rule out gonorrhea cultural methods must be undertaken The most commonly used media are chocolate agar and Pizer s media the latter being a basic medium enriched with plasma and contain ing Nile blue to inhibit other organisms The tech nique of obtaining cultures is very important and extreme care must be taken to avoid excess con tamination Moist fresh inocula must be used The cultures of gonococci can be identified easily by their color reaction to the oxidase reagent This reagent (1 per cent solution of tetramethyl p phenylenediamine hydrochloride) when po

over the suspected plate produces a deep purple discoloration of *Neisseria* colonies Best results are obtained from direct cultures of urethral prostatic or cervical exudates When these are not available cultures of the urine sediment are often of value

In culturing joint fluid for the gonococcus it is not adequate merely to streak a loopful of the material on the culture medium Preferably the plate should be flooded with about 0 5 ml of the fluid Inoculation of the sediment from centrifuged fluid is helpful Often it is possible to obtain a positive culture when joint fluid is not available by injecting a few milliliters of physiological saline solution into the periarticular structures and withdrawing some of this for culture

The complement fixation test devised by Price is of considerable value in the differential diagnosis of gonococcal arthritis particularly in cases in which a history of gonococcal infection cannot be obtained and from which gonococci cannot be recovered on culture Antibodies may appear as late as 6 weeks after the onset of arthritis and may persist for months after infection has been eradicated A changing antibody titer is considered to be diagnostic The test appears to be quite specific

Treatment With the introduction of effective chemotherapeutic agents the treatment of gonococcal infections has undergone radical changes Local therapeutic manipulations now have little place in the management of gonorrhea The sulfonamide compounds were widely used until penicillin was introduced However a large number of strains of gonococci resistant to sulfonamides have appeared after several years of such therapy and at present few gonococcal infections are cured by sulfonamides To date however only rarely have gonococci been reported resistant to penicillin The gonococcus is exceedingly susceptible to this antibiotic which at present is the drug of choice Chlortetracycline chloramphenicol and oxytetracycline are all effective in the treatment of gonorrhea However the over all results with penicillin are still better than most reported results with these agents and their use is recommended only in the case of a patient known to be sensitive to penicillin

Relatively small doses of penicillin are needed for the cure of genital infections Two injections of 300 000 units of procaine penicillin are effective in the great majority of cases If there has been no change in the character of the exudate or if gonococci persist after 3 or 4 days then the patient should be re treated with 300 000 units of procaine penicillin in a single injection Oxytetracycline or chlortetracycline in doses of 0 5 Gm initially and 0 5 Gm 6 hr later may be used for the rare case that still does not respond or for the patient with known penicillin sensitivity

A watery urethral discharge is noted in as high as 20 per cent of male patients after the gonococcus has been eradicated by penicillin This discharge is noninfective but its exact nature is not known The small doses of penicillin administered for the treatment of gonorrhea may delay the appearance of syphilitic lesions and follow up studies including serologic tests for syphilis for 6 months must be made with this fact kept in mind Studies carried out in military populations have indicated that 250 000 units of oral penicillin given a few hours after exposure serves to prevent gonorrhea There is no evidence that the development of syphilis is masked by such a dose

Penicillin is also the drug of choice in the treatment of gonococcal arthritis but the small doses that are used in cases of urethritis are inadequate for arthritis A satisfactory regimen consists of one daily injection of 600 000 units of procaine penicillin for 7 to 10 days It is not necessary to instill penicillin into the synovial cavities since this antibiotic diffuses readily into the joint spaces The response to chemotherapy is often not striking and 5 to 7 days may be required for the temperature to return to normal In many cases the arthritis does not subside completely and may smolder for a period of months with occasional exacerbations accompanied by further heat and swelling Occasionally during the course of penicillin therapy joints not previously involved become distended with fluid Many authors feel that this syndrome represents rheumatoid arthritis precipitated or aggravated by the gonococcal infection the writer prefers to regard it as a manifestation of gonococcal arthritis

Physical therapy is an important adjunct in the management of gonococcal arthritis The acutely inflamed joint should be splinted to avoid contractures The judicious use of heat gentle massage and early guarded passive motion are similarly advised in selected cases Artificial fever therapy may be of value in cases resistant to chemotherapy Removal of fluid from distended joints often affords marked relief from pain

Penicillin is also the drug of choice for *other complications* of gonorrhea It has been used locally in ophthalmia neonatorum The dose and duration of therapy must be suited to the syndrome

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seen in this condition and liver abscess is one of its complications

Omphalitis Infection of the umbilical stump in newborn infants by colon bacilli can lead to bacteremia (Winckel s disease) that is usually fatal

Bacteremia While organisms can invade the blood in almost any type of coliform infection bacteremia is especially common in pyelonephritis It usually begins with a rigor and high fever Most patients are prostrated slight icterus is not uncommon and even after a single transient episode hypotension of several hours duration is often observed Profound circulatory collapse is more likely to occur in patients with bacteremia due to gram negative organisms including the coliform bacilli *Pseudomonas Proteus Salmonella* and others (see Meningococcemia p 871) than with gram positive species Shock is more frequent in older individuals and is a poor prognostic sign There is no specific treatment moderate amounts of blood or plasma pressor amines such as Levophed or Neo-synephrine and adrenal steroids can be given but these measure should not lead to neglect of the important procedure of initiating vigorous antibacterial therapy Circulatory collapse is sometimes the first sign of coliform bacteremia and especially in patients with diabetes known urinary tract infection history of recent abortion or blood dyscrasias such as leukemia the sudden onset of shock should call to mind the possibility of infection

Escherichia coli bacteremia is occasionally seen in patients with hepatic cirrhosis in the absence of any obvious primary focus of infection The mechanism of entry of the organisms into the blood in these patients is unknown

Pyogenic Infections Coliform organisms are capable of producing abscesses in various parts of the body (see p 958) Diabetic patients are particularly prone to infection by these organisms and small abscesses at the sites of insulin injections are sometimes seen Coliform infection frequently complicates and greatly worsens ischemic gangrene of the extremities An interesting and important feature of coliform infections and abscesses in diabetes (and occasionally in nondiabetic patients) is the production of large amounts of gas in the tissues crepitation is often detectable and the gas may be visualized by x ray It has been suggested that the gas production is related to high glucose content of diabetic tissues An erroneous diagnosis of clostridial infection is often made in these circumstances

Gastrointestinal Disease There are several good epidemiologic studies incriminating certain strains of *E coli* in the etiology of outbreaks of neonatal diarrhea In several outbreaks of adult gastroenteritis there has been highly suggestive evidence that a paracolon bacillus produced the illness In view of the close resemblance of some paracolon bacilli to the *Salmonella* group it is not surprising that occasional strains might produce gastroenteritis in man

Treatment The management of bacteremic shock has been discussed The incision and drainage of localized suppurations is important in coliform infections The general measures for pyelonephritis are discussed on p 969

A variety of chemotherapeutic agents is available but none is regularly effective against all coliform bacilli and in any serious infection the drugs should be chosen with the guidance of sensitivity tests of the infecting strain Chloramphenicol or the tetracycline derivatives in an oral dosage of 2 Gm daily alone or in combination with 1 to 2 Gm streptomycin intramuscularly is likely to be effective Nitrofurantoin (p 824) and the sulfonamides are sometimes effective for urinary tract infections Neomycin (p 823) is toxic but is usually highly effective against organisms of this group and is worth using in any serious uncontrolled infection

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Section 4 Infections Due to Enteric Gram-negative Bacilli

117 COLIFORM BACTERIAL INFECTIONS

Ivan L Bennett Jr

Etiology The coliform bacteria are gram negative bacilli which normally inhabit the human intestinal tract similar organisms that occur in soil or vegetation are often included in the group The best known coliform bacilli are *Escherichia coli* (the colon bacillus) and *Aerobacter aerogenes* These two species ferment lactose and although they are harmless saprophytes in the intestinal tract both are capable of producing severe infections if introduced into other tissues The ability to ferment lactose was formerly regarded as an important differentiating characteristic between the saprophytic coliforms and the nonlactose fermenting enteric pathogens of the *Salmonella* and *Shigella* groups It is still a useful property in the laboratory but it is now recognized that there is no sharp dividing line between pathogenic and nonpathogenic species but rather there is a gradual biochemical and antigenic transition through an intermediate group of organisms the paracolon bacilli The paracolon group includes organisms that ferment lactose slowly or not at all the so called Arizona Ballerup Bethesda and Providence bacteria are paracolon bacilli Biochemically or even serologically many of them are extremely difficult to distinguish from *Salmonella* species The paracolon bacilli can produce pyogenic infections in extraintestinal sites and in addition accumulating evidence indicates that some species are capable of producing gastroenteritis in man

The tests commonly employed in differentiating the members of the coliform group are sugar fermentation the Voges Proskauer reaction methyl red test citrate utilization and serologic identification *Alcaligenes fecalis* is another normal coliform inhabitant of the bowel which does not ferment lactose and is sometimes confused with enteric pathogens on SS or desoxycholate agar plates

Because the types of infections produced and susceptibilities to chemotherapeutic agents are closely similar for *E coli* and *A aerogenes* it is customary in many clinical laboratories to report a culture as containing coli aerogenes" bacilli without differentiating between them biochemically

The presence of coliform organisms in water or feces is regarded as presumptive evidence of fecal contamination in public health and sanitary bacteriologic testing

Pathogenesis Coliform organisms may be transported from the intestinal tract to other parts of the body by way of the lymphatic vessels or blood stream or they may be spread by fecal contamination Histologically the lesions produced in various body tissues show typical acute inflammation with pus and abscess formation There is a common misconception that coliform bacterial infections are characterized by a foul smelling feculent exudate Such an odor is caused by other bacteria especially anaerobic streptococci or *Bacteroides* species which are often associated with coliform bacteria in mixed infections

Manifestations *Urinary Tract Infections* Coliform bacilli are the commonest infecting agents in pyelonephritis and cystitis The route by which these organisms reach the urinary tract from the bowel is usually by introduction into the urethra often by catheters or other instruments The frequency of pyelonephritis in young girls is believed to be accounted for by the combination of a short urethra and fecal soiling The pathogenesis clinical manifestations complications and treatment of pyelonephritis are discussed in detail beginning on p 967

Appendicitis and Peritonitis Coliform organisms can nearly always be cultured from the exudate of an appendiceal infection from diverticulitis and from the peritoneal exudate after perforation of a viscus Often they are found in mixed culture with anaerobic streptococci and clostridia It is difficult to assess the role of various bacteria in mixed infections of this type but there is little doubt about the ability of coliforms to infect serous cavities

Biliary Tract Infections Coliform bacilli are the common etiologic agents in obstructive cholangitis So-called Charcot s intermittent fever may be

grenous and eventually slough out to produce ulcers

Destructive gangrenous lesions of the lips and mouth—sometimes called noma—which occasionally occur in chronically ill or malnourished children are apparently associated with spreading infection due to *Pseudomonas*

Treatment The tendency of these infections to occur in damaged ischemic and fibrotic areas or in persons already debilitated makes their therapy difficult Improvement of the patient s general condition may help to eradicate a local infection Urinary infections may subside after surgical removal of obstructive lesions Debridement of devitalized tissues and better drainage of chronic infections are desirable Sulfonamides are partially effective but unfortunately not all strains of *Proteus* and *Pseudomonas* are susceptible to these drugs The discontinuing of ineffective antibiotic therapy permitting reestablishment of normal relationships between the bacterial flora of the body may help to terminate superinfections by these organisms

The selection of a specific chemotherapeutic agent should be made on the basis of sensitivity tests A combination of streptomycin 1 to 2 Gm daily with chloramphenicol or one of the tetracycline drugs is sometimes effective *Proteus* and *Pseudomonas* are irregularly susceptible to neomycin but this drug is very effective against many strains

Most but not all *Pseudomonas* strains are susceptible to polymyxin B This drug in a daily intramuscular dosage of 200 to 500 mg sometimes is lifesaving but when it is used the patient should be observed carefully for renal damage (p 823) Superficial *Pseudomonas* infections (burns external otitis eye) can be treated by local application of polymyxin as a solution or an ointment One per cent acetic acid and nitrofurazone ointment can also be used for surface infections

Many strains of *Proteus* are relatively susceptible to penicillin and successful use of massive doses of this drug (10 to 100 million units daily) has been reported frequently enough that this regimen is well worth trying in life threatening infections Novobiocin is also effective against occasional strain of *Proteus*

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119 BACTEROIDES INFECTIONS

Paul B Beeson

Etiology The genus *Bacteroides* includes a group of gram negative non spore bearing anaerobic bacilli Members of this genus are normally found among the flora of the mouth intestinal tract and vagina The species of greatest interest from the standpoint of human infections is *Bacteroides funduliformis* also called *Bacillus fundiliformis* and *Fusiformis necrophorus*

Pathogenesis *Bacteroides* infections probably occur more commonly than is indicated by published case reports Some of them go unrecognized because of the difficulties associated with isolation and identification of anaerobes The usual source of infection is presumed to be the alimentary tract of the host Organisms may be transported to other parts of the body by direct extension or by way of the blood and lymph Members of the genus have been isolated from many different types of infections including tonsillitis otitis media lung abscess empyema arthritis appendicitis peritonitis endometritis pyelonephritis and subacute bacterial endocarditis Usually other intestinal bacteria such as *Escherichia coli* *Clostridium welchii* and anaerobic streptococci are present in addition to the *Bacteroides* From such mixed infections however *Bacteroides* may invade the blood stream and be transported elsewhere producing metastatic infections especially in the lungs joints and liver The septicemic form of *Bacteroides* infection occurs most frequently when thrombophlebitis develops in the vicinity of the primary infection

Manifestations In mixed infections such as otitis media appendical abscess etc the course and symptoms are variable and the role of the *Bacteroides* cannot be evaluated The outcome in

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118 *PROTEUS* AND *PSEUDOMONAS* INFECTIONS

Ivan L Bennett Jr

Etiology The *Proteus* genus consists of a group of gram negative motile bacilli which ferment dextrose and sucrose but do not act upon lactose or mannite They split urea producing ammonia The several varieties differ in other biochemical and in serologic reactions One group (X) possesses an antigen similar to that present in certain rickettsiae this probably accounts for the appearance of *Proteus* antibodies (Weil Felix reaction) in certain rickettsial diseases *Proteus vulgaris* *P morganii* and *P rettgeri* are the most common species infecting man

The *Pseudomonas* group of organisms are gram negative motile bacilli which do not ferment carbohydrate and which produce distinctive pigments The clinically important variety is *Ps aeruginosa* often called *Bacillus pyocyaneus* Coloring of exudates by its pigment has caused the organism to be designated as "the bacillus of blue green pus" *Pseudomonas* and *Proteus* bacilli are normal inhabitants of the mouth intestinal tract and skin of human beings *Proteus* and *Pseudomonas* are among the most resistant of common bacteria to antibiotic agents in general use and infection by them is becoming a serious problem in many parts of the world

Pathogenesis *Proteus* and *Pseudomonas* infections are often the result of implantation of the organisms in an already damaged tissue Ordinarily these infections remain limited to one area but particularly in burns or chronic ulcers and sinus tracts the organisms may be disseminated in the blood stream to form metastatic pyogenic infections elsewhere Histologically the lesions of *Pseudomonas* are characterized by thrombosis of small arteries this may produce areas of infarction in which there is little inflammatory reaction or cellular exudation The lesions caused by *Proteus* bacilli show the typical changes of acute inflammation and abscess formation

Because the growth of *Proteus* and *Pseudomonas* is seldom restrained by the administration of antibiotics they often come to dominate the "normal flora" of patients undergoing treatment for some other infection or receiving prophylactic chemotherapy As a result superinfection" (p 829) of the urinary tract middle ear lung etc by these bacilli is becoming an increasingly frequent complication of antibacterial therapy Indeed in many areas nosocomial infection by *Proteus* and *Pseudomonas* is as great a problem as that caused by antibiotic resistant staphylococci

Manifestations *Pseudomonas* and *Proteus* infections can occur in many locations including skin, subcutaneous tissue bone synovial cavities lung kidney meninges ear mastoid cells and paranasal sinuses The most important of these are

Urinary Tract Infections *Pseudomonas* and the *Proteus* bacilli are among the commonest pathogens of the urinary tract It is not unusual for both kinds of organisms to be present at the same time in chronic urinary tract infections or one of them may be present in combination with some other pathogen such as a member of the coliform group See p 967 for a discussion of pyelonephritis

Infections of the Ear, Mastoid, and Paranasal Sinuses *Pseudomonas* and *Proteus* are frequent secondary invaders in infections of these areas They usually occur in combination with gram positive cocci A chronic infection of the external auditory canal due to *Pseudomonas* is sometimes a troublesome ailment causing considerable discomfort and discharge It may lead to thickening of the eardrum and impairment of hearing

Infections of the Eye *Pseudomonas* may become implanted on abrasions of the cornea and may produce an infected ulceration The infection then is likely to spread into the eyeball This is one of the most severe ophthalmic infections and can lead to destruction of the eyeball

Infections of the Skin and Subcutaneous Tissues Chronic ulcerations of the skin such as varicose or decubitus ulcers are very frequently contaminated with *Pseudomonas* and *Proteus* organisms The same is true of burned areas Draining sinuses in chronic osteomyelitis are also susceptible to this type of secondary bacterial infection

Meningitis Primary meningitis caused by these organisms does not occur They may however be introduced into the subarachnoid space in the course of a lumbar puncture or spinal anesthesia or by extension from a focus of infection in the mastoid cells or paranasal sinuses The resulting meningitis is very severe and often fatal

Bacteremia In debilitated persons particularly premature infants and in patients with blood dyscrasias or lymphomas local *Pseudomonas* or *Proteus* infections can lead to bacteremia and a fulminating illness with hectic fever and secondary abscesses which often ends fatally *Pseudomonas* sepsis may be accompanied by a unique skin eruption consisting of vesicular or bullous lesions filled with clear fluid The vesicles rupture a day or two after their appearance the bases then become gan

to those of pneumococci in fact serologic cross reactions occur between certain Friedlander strains and pneumococci Friedlander bacilli have been divided serologically into groups A B C D and E and a heterogeneous group X Most infections in human beings are due to members of group A

Pathogenesis Infections of the urinary and biliary tracts the peritoneal cavity and other serous membranes comprise the bulk of diseases caused by the Friedlander bacilli These are similar in manifestations and pathogenesis to those produced by the coliform organisms discussed on p 878 In the lungs however Friedlander infections take the form of an acute rapidly progressive and often fatal pneumonia or of a chronic lung disease with bronchitis bronchiectasis and cavity formation

Manifestations As already mentioned the majority of infections caused by the Friedlander bacilli are similar to those due to the coliform bacteria Thus Friedlander bacilli may be among the infecting organisms in general peritonitis or they may be the etiologic agents in pyelonephritis or cholangitis Occasionally they cause infections of the middle ear mastoids or paranasal sinuses or meningitis secondary to one of these A significant proportion of all reported cases of Friedlander bacillus meningitis has involved persons with diabetes mellitus Another kind of Friedlander bacillus meningitis is that which complicates traumatic perforation of the skull or spinal canal especially as encountered in war wounds

Acute Pneumonia About 1 per cent of all cases of bacterial pneumonia are caused by Friedlander bacilli The disease is most common in males over forty years of age and is frequent in alcoholic addicts The manifestations are similar to those of pneumococcal pneumonia with sudden onset of chills fever and severe pleuritic pain Patients are more likely to be delirious and prostrated and fever is more often remittent than in pneumococcal pneumonia In about half the cases the sputum is dark brown or red and is so sticky that the patient has difficulty in expelling it from his mouth and lips The pulmonary lesion usually progresses rapidly spreading from lobe to lobe and from one lung to the other within a few days Cyanosis and dyspnea develop rapidly and jaundice vomiting and diarrhea are often present Although x rays may show extensive consolidation in the lungs physical signs may be deceptively few The blood leukocyte count may be elevated but is often low or in the normal range Lung abscess and empyema are frequent complications Previous to the introduction of sulfonamides and streptomycin the fatality rate reported in different clinics varied from 50 to 80 per cent death within 48 hr was not infrequent

Chronic Infection of the Lung This may follow acute Friedlander pneumonia but is also seen in patients who give no history of acute onset The principal manifestations are productive cough weakness and anemia Hemoptysis is not common Chronic empyema or sterile serous effusion is observed in about one fourth the cases Cavity formation frequently occurs and is usually located in the upper lung fields There is very little inflammatory reaction around the cavities so that in roentgenograms they appear to have thin walls A number of patients with chronic Friedlander infection of the lung have had an erroneous diagnosis of pulmonary tuberculosis and have been given sanatorium treatment The course of this disease is quite variable Some cases have been observed for 10 or 20 years with very little change in symptoms and signs whereas others have shown gradual improvement after several months

Diagnosis Diagnosis can be made only by the isolation of Friedlander bacilli A presumptive diagnosis of Friedlander pneumonia can be made on the basis of Gram stain of the sputum this shows numerous short plump gram negative bacilli each surrounded by a clear space because of the capsule In any patient with acute pneumonia whose sputum is found to contain a predominance of gram negative bacilli a presumptive diagnosis of Friedlander infection should be made and appropriate therapy instituted Culture of the sputum on a solid medium shows almost pure growth of Friedlander colonies Certain proof is afforded by isolation of the organisms from the blood pleural exudate or fluid aspirated from the lung

Treatment In view of the age group involved and the frequent association with alcoholism and malnutrition the fatality rate in acute Friedlander pneumonia will doubtless remain fairly high—i e 25 to 50 per cent Specific antiserums have been employed in the treatment of acute Friedlander pneumonia but the results have not been encouraging In vitro Friedlander bacilli are usually susceptible to sulfonamides streptomycin chlortetracycline and chloramphenicol and results of therapy of experimental Friedlander infections with all these agents have been quite satisfactory The best regimen employs streptomycin in large doses (3 to 4 Gm daily) with chloramphenicol or a tetracycline Resistance to streptomycin develops rapidly and if the response is satisfactory the dose can be reduced or it can be discontinued after 3 to 5 days Chloramphenicol or tetracycline should be continued for a minimum of 10 to 14 days

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these cases usually depends on the possibility of surgical treatment

Septicemia Following Tonsillar Infection A characteristic disease pattern may be encountered in primary *Bacteroides* infection of the tonsils The patient usually suffers from sore throat for a few days then abruptly becomes extremely ill A hectic type of fever ranging between 101 and 104 F is common and temperature elevations to 106 to 108 F may occur Signs of acute inflammation in the tonsils and pharynx may have subsided but there is usually tenderness in the region of the tonsillar lymph nodes Palpation along the course of one of the internal jugular veins discloses a firm tender cord indicating the presence of a thrombus Septic emboli become lodged in the lungs forming *lung abscesses* and pleural *empyema* may develop Productive cough and pleuritic pain are common at this stage Purulent *arthritis* may develop in one of the large joints e g the elbow shoulder knee or ankle The liver becomes enlarged and tender as a result of acute hepatitis and there may be *icterus* Without appropriate therapy this form of *Bacteroides* infection usually causes death within a few days

Post partum and Postabortal Infection *Bacteriodes* septicemia similar to that which complicates tonsillar infection is occasionally encountered in the post partum or post abortal state Here the primary infection is endometritis with thrombophlebitis in the pelvic veins The manifestations are similar to those just described including septic fever pulmonary symptoms arthritis icterus and hepatitis

Laboratory Findings There is usually a leukocytosis ranging from 12 000 to 25 000 Patients with hepatitis have elevated serum bilirubin and a positive test for bilirubin in the urine but the stools do not become acholic The only method of specific diagnosis is demonstration of *Bacteroides* by cultural methods As already mentioned the organisms are often associated with other bacteria common to the gastrointestinal tract and this makes cultural demonstration technically difficult In bacteremia or metastatic infections however *Bacteroides* can be isolated relatively easily provided that incubation is carried out under anaerobic conditions Thioglycollate broth is suitable The possibility of this type of infection should be considered in appropriate cases and anaerobic cultures made After 1 or 2 weeks it is possible to make a diagnosis by demonstration of a rising titer of agglutinins for stock strains of *Bacteroides* organisms

Treatment Because of the likelihood of mixed infection chemotherapy must be given with a view to the entire picture *Bacteroides* infections have shown little response to sulfonamides or penicillin but there are many reports of favorable outcome following administration of Aureomycin (chlortetracycline) and this appears to be the drug of first choice In view of the tendency to rapid necrosis of tissue with formation of abscesses in which the bacteria are protected from the action of phagocytes chemotherapy alone will not always be successful For this reason a vigilant watch should be kept for signs of abscess or empyema which can be evacuated surgically

Prognosis In mixed local infections the course is variable The fatality rate of septicemic cases formerly was almost 100 per cent but a very considerable reduction has been effected since the introduction of chlortetracycline therapy

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120 FRIEDLANDER BACILLUS (KLEBSIELLA) INFECTIONS

Ivan L Bennett Jr

Etiology The Friedlander bacilli (*Klebsiella pneumoniae* or *friedlanderi*) are encapsulated gram negative bacilli found among the normal flora of the mouth and respiratory and intestinal tracts They are closely related to *Acrobacter aerogenes* and cannot be differentiated by biochemical reactions Indeed there is general agreement that separation of the *Aerobacter* genus from *Klebsiella* is not justified although clinical usage will continue to refer to the strains from the respiratory tract as Friedlander bacilli and those from other regions as *Aerobacter* The *Klebsiella* isolated from respiratory infections usually form large mucoid colonies on solid media and are virulent for mice These characteristics however are not invariable enough to differentiate them from intestinal strains The capsular polysaccharides of Friedlander bacilli are similar

to those of pneumococci in fact serologic cross reactions occur between certain Friedlander strains and pneumococci Friedlander bacilli have been divided serologically into groups A B C D and E and a heterogeneous group X Most infections in human beings are due to members of group A

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121 TYPHOID FEVER

Paul B Beeson

Definition Typhoid fever is a febrile illness of several weeks duration due to infection with *Salmonella typhosa* and characterized by fever cough headache skin eruption splenomegaly and leukopenia

History Descriptions of typhoidlike illnesses have been given since ancient times The name typhoid fever was first used by French clinicians in the early part of the nineteenth century In 1836 Gerhard of Philadelphia presented the first satisfactory clinical differentiation between typhoid and typhus fevers Between 1855 and 1870 Budd an English practitioner studied the epidemiology of the disease and correctly concluded that the source of contagion was the fecal discharges of affected persons In 1880 Eberth isolated the typhoid bacillus

Typhoid fever has been a prominent disease of military groups and was an important cause of disability and death in wars previous to the First World War Between 1900 and 1910 prophylactic vaccination was developed and the use of this procedure in the First World War reduced the incidence of the disease remarkably As a result of widespread prophylactic vaccination in civilian populations and of improved methods of sanitation typhoid fever is far less common now than 50 years ago The introduction of chloramphenicol therapy in 1948 brought about a drastic change in the duration and prognosis of the disease

Etiology *Salmonella typhosa* is a motile gram negative bacillus which ferments dextrose maltose and mannite without the production of gas and does not ferment lactose or sucrose At least 20 different strains of the organism have been distinguished by testing their susceptibility to lysis by bacteriophages Such typing has been of great assistance in tracing the sources of outbreaks of typhoid fever but is of no particular value to clinicians since there is no distinct difference in the character of diseases produced by the different phage types *S typhosa* has flagellar (H) antigens and somatic (O) antigens which cross react serologically with H and O antigens of certain other *Salmonella*

Epidemiology Human beings are the only known natural hosts of typhoid infection Infection is transferred from the intestinal tract of one person to the mouth of another Great epidemics have resulted from fecal contamination of water or milk supplies but modern methods of sanitation are rendering this mode of spread less common The principal source of infection now is typhoid "carriers —i e persons who have recovered from the disease but continue to harbor the causative organisms Such individuals are particularly dangerous if they are food handlers Transmission by flies is a possibility and is particularly likely to occur where outdoor toilets are used Contamination of water supplies from improperly constructed toilets can also occur Epidemics have resulted from the eating of shellfish caught in areas of sewage disposal Formerly typhoid fever was especially prevalent in the summer and early fall This may have been due to such factors as better bacterial growth in warm weather fly season and vacation travel At present however there is no marked seasonal variation cases are acquired from carriers sporadically throughout the year

Pathogenesis There can be no question that the portal of infection is the gastrointestinal tract The point at which bacteria actually enter the tissues is not so certain however It is commonly stated that the bacilli are first taken up by the lymphoid tissue of the intestinal wall especially the Peyer s patches and that drainage from there involves the mesenteric lymph nodes It has been proposed by some workers on the other hand that invasion of the tissues may occur in the pharynx and tonsils Whatever the primary point of invasion the next significant factor in the development of typhoid fever is the presence of bacilli in the circulating blood This is undoubtedly due to a constant feeding of organisms into the blood from some focus such as the mesenteric lymph nodes The bacteremia permits secondary infection of the other areas liver spleen, bone marrow and other lymph nodes At the end of the first week of infection antibodies appear in the blood and the bacteremia usually ceases From this stage onward the infection which has been established in the biliary tract is particularly important since it furnishes a flood of infected material to the upper part of the small intestine This probably is responsible for the heavy

involvement of the Peyer s patches during the sec ond and third weeks of the disease and for the pres ence of organisms in the fecal discharges

The gross autopsy findings in patients dying of typhoid fever are those of inflammatory involve ment of lymphoid tissues especially in the wall of the intestine and in the mesenteric lymph nodes and the spleen The spleen is enlarged as is the liver The Peyer s patches become swollen and may undergo necrosis leaving oval shaped ulcers these are most numerous in the terminal ileum but may extend as high as the jejunum or as low as the appendix and cecum They are responsible for the most serious complications of typhoid fever per foration and hemorrhage

The common denominator underlying typhoid lesions wherever encountered consists in a marked proliferation of large mononuclear cells derived from the reticuloendothelial system This prolifera tion encroaches on blood vessels and leads to necrosis of tissue Microscopic examination of the intestinal lesions reveals few bacilli in the extra cellular spaces most of them appear to be located within macrophages Goodpasture has reported that typhoid bacilli can also be found within plasma cells This phagocytosis may serve the parasite bet ter than the host since intracellular existence of the organisms may protect them from such agents as antibodies and drugs This may explain why the disease seems to continue without observable clin ical change after the appearance of antibodies in the blood and why signs of clinical improvement do not become manifest until 2 or 3 days after beginning chloramphenicol therapy

Because the most prominent inflammatory changes are found in the intestine there is a tendency to regard typhoid fever as a primary enteric infection A consideration of the observed facts however leads to the conclusion that the in testinal infection is largely secondary to the biliary tract infection which in turn is sequel to the initial bacteremia The fact that organisms are constantly present in the blood during the early period while they do not appear in the stools until the second or third week, speaks for an important extraintestinal focus of the infection

Manifestations The incubation period of typhoid fever in sporadic cases usually cannot be deter mined but in epidemics which have followed a single exposure the incubation periods showed con siderable variation averaging 10 to 12 days

The clinical manifestations of typhoid fever are exceedingly variable Some persons can be infected without any disability whatever some suffer only a brief febrile illness In others the disease takes the form of an overwhelming infection leading to death within a few days In the majority of cases recovery occurs after an illness of several weeks The de scription to follow will deal chiefly with cases of average severity but it should be emphasized that the clinician must always have in mind the great variability of typhoid fever

The first symptoms are usually abdominal dis comfort malaise feverishness anorexia weakness headache and cough and their onset is so insidi ous that the patient does not go to bed for several days The fever is remittent in type gradually in creasing in height until about the tenth day when it may fluctuate between 103 and 105 F This con tinues for the next 10 days or 2 weeks then the daily remissions begin to be greater and there is a gradual fall over a period of several days with fever terminating after a total period of about 30 days Chills may occur during the early part of the in fection occasionally the first sign of illnes is a chill Nosebleeds may be troublesome Bronchitis is prominent and typhoid is frequently mistaken for some form of primary pulmonary infection in the early stage Scattered fine and medium moist rales may be heard at the lung bases x ray of the chest may occasionally reveal one or more small areas of pulmonary consolidation The headache is of great severity and may be the chief complaint Curi ously herpes simplex is very rare in typhoid fever The patient is likely to suffer from abdominal dis tention and colicky pain There may be either diar rhea or constipation the latter being more frequent at the onset At the height of the disease diarrhea may supervene and numerous pea soup stools may be passed daily When the fever has reached its peak the patient may be apathetic and drowsy or he may show delirium The appearance is that of severe toxemia The typhoid patient seldom seems alert Muscular twitching and picking at the bedclothes may be noted in patients who have had prolonged high fever

The eruption usually appears during the second week The lesions which are called "rose spots" are found most often on the anterior surface of the trunk between the level of the nipples and the um bilicus They are small rose red spots 2 to 4 mm in diameter and usually have a small central peak which is palpable Their color fades completely on pressure They are not numerous usually only 6 to 12 may be seen at a time They tend to appear in crops and to disappear without leaving any discol oration When extensive they may also be present on the proximal parts of the extremities but are seldom seen on the face and practically never on the palms or soles

The spleen becomes palpable by the end of the first week in the majority of cases It is soft and may be missed if the examiner palpates too deeply It rarely extends more than 2 or 3 cm below the costal margin and recedes by the time the fever begins to subside

During the first week or two of typhoid fever the pulse rate is usually comparatively slow in relation to the fever this is sometimes of assistance in diagnosis After the third week however the pulse rate is proportional to the temperature A dicrotic pulse is often present but this is not particularly helpful in diagnosis

With the beginning of the subsidence of the fever there is gradual improvement in symptoms and a return of the patient s appetite Usually however a marked weakness persists for many days after the temperature has returned to normal

Relapse is not uncommon in typhoid Some reports indicate that the frequency is as high as 10 per cent The clinical features are similar to although milder than those of the initial illness There may be a recurrence of the bacteremia and even of the skin eruption Fatalities are uncommon during relapses

Complications *Hemorrhage from the bowel* is the most important complication of typhoid fever Gross bleeding occurs in about 20 per cent of cases This is usually during the third week of the disease at the time when the intestinal ulcerations have reached their greatest extent Severe hemorrhage is accompanied by the signs and symptoms of acute blood loss—i e rapid weak pulse low blood pressure sweating pallor and drowsiness—and by the appearance of gross blood in the stools One sign occasionally of value as an indication of massive hemorrhage is rapid fall in body temperature a decrease of 5 or 6 F in the course of a few hours

Perforation of the intestine is a very dangerous complication and one which accounts for many of the deaths in typhoid fever Fortunately it is far less common than hemorrhage (1 to 2 per cent of cases) Perforation takes place at the site of an ulcer usually in the terminal ileum but occasionally in the appendix or in the proximal part of the colon Occasionally there are multiple perforations The clinical manifestations are pain usually in the right lower quadrant followed by rigidity and diminished peristalsis Signs of free air in the peritoneal cavity may be detected The pulse rate may increase there is usually a rise in leukocyte count and the temperature may fall Diagnosis of perforation may be very difficult because of pre existing abdominal distention tenderness and pain Frequent examinations throughout the course of the disease by the attending physician assist him in recognizing and evaluating the changes which occur with perforation

Bacterial pneumonia occasionally complicates typhoid fever If suspected this can be verified by physical examination and x ray and by appropriate bacteriologic studies Many other complications of typhoid fever can be mentioned they include the various infections likely to arise in a severely ill patient such as *parotitis sinusitis conjunctivitis* etc *Thromboembolic disease* may occur *Meningitis* and *arthritis* due to *S typhosa* are rare complications

Three late sequelae of this disease deserve mention *Periostitis* may develop months or even years after the original illness It may involve almost any of the long bones or the spine The lesion is as the name implies on the outside of the bone clinically there is a tendency to abscess formation with periodic rupture through the skin and healing The second complication is *gallbladder disease* Signs of cholecystitis occasionally are noted during the acute illness Years later the subject may suffer from cholecystitis and cholelithiasis Gallbladder stones containing live typhoid bacilli are said to have been removed 20 or 30 years after the original attack of typhoid fever Finally a *chronic pyelonephritis* or *pyonephrosis* due to *S typhosa* may develop

The Carrier State Approximately 2 or 3 per cent of patients with typhoid fever can be expected to become typhoid carriers i e to continue excreting the organisms in the feces for months or years after clinical recovery In most instances the carrier state is due to persistence of infection in the biliary tract and cholecystectomy is usually effective in eradicating the condition Urinary carriers are occasionally encountered but they constitute a much less serious problem than intestinal carriers

Laboratory Findings The *leukocyte count* during the first week or two is usually in the low normal range (i e 5 000 to 8 000) during the third and fourth weeks it may become even lower (3 000 to 6 000) During convalescence there is a rise The *red blood corpuscle count* falls progressively during the course of the disease and often reaches a level of 3 000 000 to 3 500 000 in the third and fourth weeks Acute hemolytic crises have been observed The *urine* contains some albumin during the febrile stage but is otherwise not remarkable Tests for *occult blood in the feces* are usually positive from the second to the fourth week of the disease

Culture of the blood is positive for *S typhosa* during the first week of the disease in about 90 per cent of cases After that time the likelihood of a positive blood culture decreases rapidly *Culture of the feces* is rarely positive for *S typhosa* before the tenth day of the disease The incidence then increases rapidly up to the fourth week of illness the organisms can be recovered from the feces in at least 90 per cent of cases if good bacteriologic technique is employed Bismuth sulfite agar in conjunction with selenite F or tetrathionate enrichment medium gives excellent results *Culture of the urine* is positive during the third and fourth weeks in about 20 per cent of cases of typhoid fever

Examination of the blood for *specific agglutinins* (*Widal test*) usually gives a positive result at the end of 7 to 10 days of illness The titer of agglutinins rises during the next 10 days reaching a peak about the third or fourth week of illness The titer then falls gradually during the succeeding months There has been much discussion of the relative values of H and O agglutination tests in diagnosis The titer of H antibody is usually higher than that for O and the H sometimes appears a few days earlier No definite figure of certain diagnostic significance can be given As with all serologic tests a rising titer during the course of the illness is more significant than any individual figure In general titers higher than 1 160 with both antigens are probably significant and the O antigen is more specific than the H In about 10 per cent of cases the Widal test never reaches diagnostic" titers Previous immunization with typhoid vaccine has to be taken into consideration in evaluating the results of Widal tests A person who has received an immunization during the preceding 6 months would be likely to show specific agglutinins in his serum Furthermore an anamnestic response to any infection may cause the reappearance of antityphoid antibodies in the serum of a previously inoculated person

Differential Diagnosis The sporadic cases of typhoid fever seen nowadays nearly always present diagnostic problems and positive differentiation often has to wait for laboratory tests Nevertheless positive diagnosis of typhoid fever can be made by means of laboratory tests which are generally available i e culture of blood and feces and the agglutination (Widal) test Differentiation of typhoid fever from other diseases which resemble it such as the ones listed below depends in most cases upon the establishment of a *positive diagnosis of typhoid fever* Repeated negative cultures and agglutination tests should direct attention away from typhoid since it would be a rare experience to encounter typhoid fever with negative Widal test and negative cultures of blood feces and urine The following diseases should receive particular consideration

Typhus Fever The onset is usually sudden with chill followed by sustained high fever The rash is more profuse and the individual lesions are not palpable The Weil Felix test is positive

Atypical Pneumonia The insidious onset with respiratory symptoms resembles typhoid but abdominal discomfort and gastrointestinal symptoms are lacking X ray reveals a sizable area of pulmonary consolidation which is rare in early typhoid Cold agglutinins if present will bear out the diagnosis

Brucellosis The clinical picture may be indistinguishable except for absence of rose spots and the fact that the pulse rate is usually elevated in proportion to the fever Blood and feces cultures and agglutination tests will differentiate

Tularemia Rarely this disease appears in the so called typhoidal form History of contact with rabbits or squirrels or tick bite should suggest tularemia There is usually a leukocytosis The agglutination test is nearly always positive by the end of the second week Rapid improvement under streptomycin or chlortetracycline treatment points to this disease

Miliary Tuberculosis The chest x ray may not show lesions until late in the disease and occasionally is negative throughout Spinal fluid examination may be of assistance

Psittacosis The clinical resemblance to typhoid fever may be remarkable including insidious onset with cough then high remittent fever an eruption with lesions like "rose spots and splenomegaly The pneumonia is however more conspicuous than the pulmonic infection of typhoid Diagnosis of psittacosis can be made by serologic test but may not be possible until comparatively late in the course of the disease

Hodgkin s Disease When the main lymph node involvement is in the abdomen this condition may mimic typhoid fever Here again repeated negative cultures and agglutinations tests should eliminate typhoid fever from consideration The finding of large lymph nodes in the thorax or other areas will eventually lead to a correct diagnosis

Treatment Precautions should be taken to prevent spread of infection from the patient to others Attendants should wear gowns to avoid contamination of clothing and should wash their hands thoroughly with soap and water after contact with the patient or his bedclothes The principal sources of danger are the patient s dejecta The best method of disposal in localities with properly constructed sewage systems is by way of flush toilets Chemical disinfection of urine is not difficult but disinfection of fecal material is almost impossible Bedpans urinals eating utensils bedclothes and bedding should be sterilized by boiling

It has always been maintained that nursing care and general supportive treatment are of paramount importance in the treatment of typhoid fever and the disease has been used as the prototype for discussions of care of patients with febrile illnesses While these measures still deserve consideration their relative importance has shrunk substantially because of the introduction of chloramphenicol therapy

Chloramphenicol is a highly effective specific drug for the treatment of typhoid fever Bacteremia ceases within a few hours after the first dose During the next two days the patient begins to feel somewhat better although the fever shows little change

During the third or fourth day there is dramatic improvement with fall in temperature disappearance of symptoms and fading of the skin eruption The patient is now on the road to recovery

A dose of 2 Gm chloramphenicol per day administered at 6 or 8 hour intervals is adequate Treatment can be discontinued at the end of 7 days in most cases but relapse will occur occasionally necessitating a second course Relapse can be prevented in the great majority of cases by continuing chloramphenicol for 3 weeks In a few instances hemorrhage and perforation have occurred several days after apparent favorable response to chloramphenicol consequently it is desirable to keep the patient under observation for at least 2 weeks The ameliorative effect of chloramphenicol can be rendered even more spectacular by the adjuvant administration of cortisone 100 to 200 mg daily This appears to be safe and to bring about defervescence of fever and subsidence of the toxic symptoms on the first instead of the third or fourth day of treatment Cortisone should probably be discontinued after 3 or 4 days therapy with chloramphenicol being maintained for the full period as already outlined

In the event of massive intestinal bleeding the patient must be given blood transfusions Intestinal perforation has always been regarded as indication for incision and drainage and this is probably still the correct view although the question may be raised whether better results might follow conservative management with administration of large doses of penicillin and chloramphenicol

During convalescence culture of the feces and urine should be done at intervals and the patient should not be discharged until three consecutive negative cultures have been obtained In the event that cultures remain positive long after clinical recovery the patient should be instructed about the danger and health authorities should be notified before his release from the hospital Cholecystectomy is not justified until the patient has continued to excrete typhoid bacilli for at least 1 year since the carrier state may cease spontaneously during that period of time The operation will successfully eradicate the carrier state in about 90 per cent of cases Chloramphenicol therapy of typhoid carriers has not been effective Some success has been obtained by treating biliary carriers with large doses of penicillin i e 10 million units daily for 6 to 10 days This should be given a trial before resorting to surgery

Immunization Vaccination against this disease is practiced in all parts of the world and there is no question that it confers some protection although there have been numerous instances of typhoid fever among vaccinated persons who had ingested heavily contaminated food or water Vaccines contain chemically killed typhoid bacilli in suspensions of approximately one billion cells per milliliter The usual dosage schedule is 0 5 to 1 0 ml subcutaneously administered on three occasions at weekly intervals

Prognosis The fatality rate in typhoid fever before chloramphenicol was 8 to 12 per cent the greatest incidence of deaths being in young infants and in the aged Massive hemorrhage and intestinal perforation account for a considerable proportion of deaths With early institution of chloramphenicol therapy the fatality rate should not exceed 1 or 2 per cent except where the disease occurs in previously debilitated and malnourished population groups

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122 OTHER *SALMONELLA* INFECTIONS

Edward W Hook and
Ivan L Bennett Jr

Definition Although there is variation in the pathogenicity of the many different members of the *Salmonella* genus almost all are capable of producing human disease The infections in man are *acute gastroenteritis or food poisoning enteric or paratyphoid fever* which resembles typhoid clinically but is usually a milder illness *bacteremia* and a multitude of *localized infections* ranging from osteomyelitis to endocarditis

Etiology and Epidemiology The *Salmonella* are gram negative bacilli that inhabit the intestines of man and many animals and birds including mice rats cats dogs pigs chickens and ducks The organisms are motile ferment dextrose maltose and mannite with production of gas and do not utilize lactose or sucrose Accurate identification is technically complex and can be carried out only in a few typing centers but is very important for epidemiologic studies It is sometimes difficult or impossible to differentiate *Salmonella* from *Para*

colon bacilli (see p 868) in the ordinary clinical laboratory *Salmonella typhosa* (see p 884) and *S pullorum* differ from other species in failing to produce gas *Salmonella gallinarum* and *S pullorum* are nonmotile Several hundred species of *Salmonella* have been differentiated on the basis of their somatic (O) and flagellar (H) antigenic structure With rare exceptions human infection occurs by the oral route The meat of infected animals eggs of infected fowl (spray-dried powdered egg preparations often contain *Salmonella*) and food milk or water contaminated by excreta of man or animals are common sources Large epidemics of gastroenteritis are common and are not usually as explosive as those produced by staphylococcal enterotoxin (p 845) In 1953 an outbreak of more than 8 000 cases of *S typhimurium* infection in Stockholm was traced to contaminated meat from a slaughterhouse The most frequent causes of human infection in the United States are *S typhimurium S newport S oranienburg S montevideo* and *S choleraesuis* (*S suipestifer*) in that order (Saphra and Wassermann)

Human carriers of *Salmonella* are not rare many give no history of symptomatic infection The coliform bacteria of the intestinal microflora apparently exert a protective action by suppressing multiplication of *Salmonella* if the number ingested is small This suggestion is based upon the demonstration that elimination of intestinal saprophytes by giving antibiotics increases susceptibility of mice to infection with *S typhimurium* 100 000 fold *Salmonella* enteritis has been reported to complicate the administration of broad spectrum antibiotics to man (see Staphylococcal Enterocolitis p 1475) and patients convalescent from gastrointestinal surgery are known to be unusually susceptible to salmonellosis

The incidence of infection due to *Salmonella* is greatest during the summer months *Salmonella choleraesuis* infections do not follow this seasonal distribution and occur at a fairly constant rate throughout the year

Pathogenesis Multiplication of ingested organisms in the intestinal tract is followed by symptoms of food poisoning which in the majority of instances subside after a few days The intestinal irritation and inflammation are probably produced by true infection of the mucosa and penetration of the intestinal wall with resulting transient bacteremia or more serious systemic illness occurs in a few patients The invasive potential of the bacteria and the resistance of the infected host determine the course of events after *Salmonella* have gained access to the gastrointestinal tract For example about 50 per cent of *S choleraesuis* infections are accompanied by bacteremia and the mortality rate is about 20 per cent The infrequent occurrence of gastroenteritis and a carrier state due to *S choleraesuis* also reflects the invasiveness of this organism Bacteremia is unusual in infections produced by most other species the mortality is much lower and the carrier rate is higher

Patients with debilitating disorders of many types are unusually susceptible to severe *Salmonella* infections Another disease is present in about one half the patients who develop sporadic infection Deaths from bartonellosis or Oroya fever (p 915) are often the result of *Salmonella* bacteremia Invasion of the blood stream by these bacteria also occurs in viral hepatitis thalassemia leukemia and cirrhosis of the liver In these last two conditions *Salmonella* bacteremia is probably a reflection of a general increase in susceptibility to infection by gram negative enteric bacteria Relapsing fever (p 1017) is sometimes complicated by salmonellosis and patients with sickle cell anemia are peculiarly susceptible to *Salmonella* osteomyelitis Patients with tumors of various types may develop *Salmonella* bacteremia and in several reported instances the neoplasm itself has been the seat of localized suppuration

With the development of systemic infection there may be histologic changes similar to those of typhoid fever (p 884) or multiple foci of suppuration in bone joints endocardium pleura meninges etc

Clinical Manifestations *Salmonella Food Poisoning* Gastroenteritis often occurs in epidemics among individuals who have partaken of the same contaminated food although sporadic cases are not infrequent After an incubation period of 8 to 48 hr there is sudden onset of colicky abdominal pain and loose watery diarrhea occasionally with mucus or blood Nausea and vomiting are frequent but are rarely severe or protracted Fever of 101 to 102 F is common and there may be an initial chill Symptoms usually subside promptly within 2 to 5 days and recovery is uneventful Fatalities rarely exceed 1 or 2 per cent of the affected population and are limited almost entirely to infants the aged and debilitated patients

The causative organisms can often be isolated from the suspected food and from feces during the acute illness Stool cultures usually become negative for *Salmonella* within a few days but it is not unusual for patients to continue to excrete organisms for weeks or months The blood leukocyte count is usually normal

Enteric or Paratyphoid Fever Certain species can produce an illness which is clinically indistinguishable from typhoid fever i e a prolonged febrile illness with rose spots splenomegaly leukopenia gastrointestinal symptoms and positive blood and stool cultures (see p 884) The organisms most likely to produce this picture are *S paratyphi*

A S paratyphi B (*S schottmuelleri*) and *S choleraesuis* (*S suipestifer*) Occasionally a typical attack of food poisoning is followed in a few days by paratyphoid fever Generally paratyphoid fevers tend to be milder than *S typhosa* infections but differentiation on clinical grounds alone is not possible in the individual case Recovery may be followed by continued excretion of the causative organism in the stools for several months although the carrier state is less frequent and less prolonged than in typhoid

Bacteremia *Salmonella choleraesuis* (*S suipestifer*) is the species most likely to produce bacteremia but prolonged illness with positive blood cultures has also resulted from infection with many other types particularly in patients with another debilitating illness Although symptoms of gastroenteritis can precede bacteremia they are usually lacking and most cases arise sporadically In many instances the only manifestations are prolonged fever sometimes low grade but often spiking and accompanied by repeated rigors sweats aching anorexia and weight loss The characteristic features of typhoid and paratyphoid fever such as rose spots persistent leukopenia and sustained fever are absent Stool cultures are usually negative Discharge of organisms into the blood stream is intermittent (in contrast to the constant bacteremia of typhoid paratyphoid) and repeated blood cultures are often required to demonstrate the causative organism At some time early or late in the course of the illness localizing signs of infection appear in one fourth the cases Pulmonary infection in the form of bronchopneumonia or abscess pleurisy empyema pericarditis endocarditis pyelonephritis meningitis osteomyelitis and arthritis are relatively common The blood leukocyte count is usually normal but with the development of focal lesions polymorphonuclear leukocytosis as high as 20 000 to 25 000 per cubic millimeter occurs *Salmonella* bacteremia can be a very puzzling disorder especially before localization takes place and should be considered in cases of fever of unknown origin

Local Pyogenic Infections In addition to the suppurative lesions already mentioned *Salmonella* organisms can produce abscesses in almost any anatomic site These can occur independently of previous symptoms of gastroenteritis or other illness or as complications of bacteremias There is nothing characteristic about the suppurative lesions and the correct etiologic diagnosis is rarely made on the basis of clinical findings alone Meningeal localization of *Salmonella* infection is common in newborns and infants and occasional small outbreaks of *Salmonella* infection in nurseries have consisted entirely of cases of meningitis

Diagnosis Febrile gastroenteritis produced by presumed viral agents (see p 1105) and shigellosis can be distinguished from *Salmonella* food poisoning only by appropriate stool cultures in most instances especially in sporadic cases The bacteriologic methods are described on p 892 Staphylococcal food poisoning is usually an afebrile disease and vomiting is a more prominent feature than in most *Salmonella* infections Many toxic agents and drugs can produce diarrhea nausea and abdominal pain but fever is rarely a feature of these disorders and the diagnosis depends upon history of exposure or ingestion

The diagnosis of paratyphoid fever or *Salmonella* bacteremia depends upon isolation of the causative organism Agglutination tests with acute and convalescent serum as performed in the usual clinical laboratory are usually not very helpful

Treatment The treatment of *Salmonella* food poisoning is supportive Dehydration should be corrected by parenteral administration of fluids and electrolytes The abdominal cramps and diarrhea can be alleviated by small doses of morphine or paregoric and are frequently much improved if the patient takes nothing by mouth for 8 to 12 hr There is no evidence that antimicrobial drugs modify the course of the disease

Chloramphenicol is the antibiotic of choice in systemic infections the dosage being 2 to 4 Gm daily Its effectiveness is variable and unpredictable The tetracycline derivatives have sometimes appeared to exert a beneficial effect but streptomycin polymyxin neomycin and the sulfonamides are generally ineffective Occasional dramatic results have been obtained with massive doses of penicillin (40 to 100 million units daily) and this should be tried in any patient who is seriously ill with endocarditis meningitis etc

Antibiotic therapy is usually ineffective in terminating the carrier state in persons continuing to excrete *Salmonella* months after an acute illness Cholecystectomy is often effective in eradicating the carrier state in patients with gallbladder disease

Surgically accessible suppurative lesions should be drained

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123 BACILLARY DYSENTERY (*SHIGELLA* INFECTIONS)

Ivan L Bennett Jr

Definition With rare exceptions human infection by bacteria of the genus *Shigella* (often called the dysentery bacilli) is limited to the intestinal tract and is characterized by fever abdominal pain and diarrhea In clinical practice this disease is usually called bacillary dysentery a preferable term is shigellosis but this has not achieved wide usage

Etiology The *Shigella* are short nonmotile gram negative bacilli which either fail to ferment lactose or do so only slowly Their biochemical characteristics are sufficiently constant to serve as a reliable guide in identification although definitive typing into species is dependent upon complex antigenic analysis There is considerable confusion about the nomenclature of this genus The official classification (Kauffmann) consists of group A the *Shigella* unable to ferment mannite and groups B C and D the mannite fermenters There are several numerically designated types in each group The organisms are still widely referred to by earlier terminology The most important species from a clinical viewpoint are *Shigella shigae* (*Sh dysenteriae* the Shiga Kruse bacillus) *Sh flexneri* (*Sh paradysenteriae*) *Sh boydii* and *Sh sonnei* Two species *Sh alkalescens* and *Sh dispar* are almost never associated with outbreaks of diarrheal disease and are thought by many to be better classified as saprophytic coliforms than as enteric pathogens Isolation of either from the stool of a patient with diarrhea does not establish a diagnosis of bacillary dysentery

Shigella shigae contains a substance that is neurotoxic for animals and resembles a true exotoxin Evidence for a significant role of this toxin in human disease is lacking All *Shigella* possess endotoxins similar to those of gram negative bacilli in general but the manifestations of bacillary dysentery cannot be attributed to these substances either

Epidemiology In contrast to the *Salmonella* group which is widespread throughout the animal kingdom *Shigella* live primarily in the gut of man although monkeys and rarely dogs may excrete the organisms The convalescent or asymptomatic carrier is the principal reservoir of the disease The only important route of spread is fecal oral transmission is indirect by means of food utensils towels etc Watt and Hardy have conducted cultural surveys in this country and have found carrier rates ranging from 10 per cent of the population in certain parts of New Mexico to 0 1 per cent in New York City Studies such as that of Philbrook have shown that excretion of *Shigella* by carriers is so intermittent that practically speaking their detection and treatment on any large scale is impossible

In regions of the world where sanitation is poor and under conditions such as mobilization of troops in the field epidemics of dysentery are common Outbreaks are rarely explosive but develop over a period of several weeks The ability of some *Shigella* strains to survive in sea water for 3 days was shown by Cheever to be responsible for ship to ship spread of dysentery among naval personnel Flies can transmit the infection by mechanical contamination and in warm climates where sewerage is poor the number of cases of dysentery parallels the fly count In such circumstances fly control becomes an important measure in prevention

In the civilized countries of the world large outbreaks of *Shigella* are now rare with the exception of so called asylum dysentery occurring in mental institutions and orphanages where there are close contact and unusual opportunity for fecal soiling among the feebleminded or youthful inmates

Pathogenesis The monkey is the only laboratory animal in which *Shigella* dysentery can be produced with regularity In volunteer studies it has required the ingestion of surprisingly large numbers of bacilli to establish infection in man

Multiplication of ingested bacilli in the intestinal tract is followed by a diffuse enteritis The rectum and sigmoid are almost always involved and in severe cases the entire colon and terminal ileum may be diseased The infection remains localized in the intestinal wall there being no tendency to invasion of the blood stream or biliary tract as in typhoid fever or other *Salmonella* infections The lumen of the affected segments is covered by a fibrinous exudate containing large numbers of neutrophils and as necrosis of mucosal cells develops superficial ulcerations that bleed easily appear In severe case the ulcers enlarge and coalesce until only a few scattered patches of intact mucosa remain on the raw and inflamed surface While the inflammatory process sometimes involves the submucosa and muscularis with resulting edema and thickening of the intestinal wall perforation is very rare The systemic effects of the disease result al

most entirely from losses of fluid and electrolytes with the diarrhea

Even in untreated cases spontaneous recovery usually occurs within a few days with rapid restoration of the intestinal mucosa to normal The mechanism of this is not known It is clearly unrelated to antibody formation and the suggestion that bacteriophage may be involved is entirely without evidence

Relapses are sometimes seen and second attacks are not infrequent These are again unrelated to serum antibody levels Residency in endemic areas in the tropics is well known to lead to resistance to clinically apparent attacks of bacillary dysentery The basis for this seasoning is also unknown

Manifestations The incubation period is usually 24 to 48 hr Colicky abdominal pain is followed within an hour by profuse diarrhea Fever up to 104 F occasionally with chills occurs and nausea and vomiting headache and malaise develop rapidly Stools are watery greenish and irritating and contain shreds of mucus and often flecks of blood In a few patients there may be profuse bleeding Tenesmus and straining are prominent accompaniments of the diarrhea Depending upon fluid losses the patient may become profoundly dehydrated and circulatory collapse can occur especially in elderly or debilitated patients There is generalized abdominal tenderness without rigidity or localizing signs Rarely the spleen is palpable Sigmoidoscopic examination reveals diffuse mucosal inflammation often with multiple ulcerations The ulcers are not so large or so sharply demarcated as those of amebic colitis and in amebiasis the intervening mucosa is usually uninflamed

Spontaneous recovery within 2 to 7 days is usual with relapses in about 10 per cent of the cases unless chemotherapy is given Children under two years of age and elderly individuals are usually more severely ill and the mortality rate is highest in these groups

Shigella shigae produces the severest infections mortality rates of 25 to 50 per cent have been recorded in epidemics produced by this species which is fortunately very uncommon in the United States

Chronic bacillary dysentery is virtually unheard of in this country but it is said to occur in the tropics especially after Shiga infections The role of reinfection in such cases has not been evaluated and many of these cases probably represent amebic infections Patients may continue to shed *Shigella* after convalescence the true incidence of the carrier state is probably higher than has been realized in view of the intermittency with which positive cultures are obtained in carefully controlled follow up studies

Complications include acute *arthritis* usually involving a single large weight bearing joint during convalescence Joint fluid is sterile This complication is unusual in patients given chemotherapy and is most likely to follow infections with *Sh shigae* which have a protracted course *Reiter s syndrome* the triad of arthritis conjunctivitis and urethritis is thought by some to be a sequel of *Shigella* infections This is discussed on p 1154

There is no convincing evidence to support the assertion that bacillary dysentery and chronic ulcerative colitis are etiologically related

A few instances of perforation of the colon have been reported *Shigella* organisms have been isolated from abscesses but this is very uncommon *Shigella alkalescens* has been reported as the causative agent in acute pyelonephritis and has been isolated from the blood in rare instances many of these infections have been in children

Laboratory Findings The blood leukocyte count in bacillary dysentery is normal Changes in erythrocytes and urine are secondary to dehydration Microscopic examination of the stool reveals shreds of mucus erythrocytes and polymorphonuclear leukocytes Pus cells are not characteristic of the stools in amebiasis although they occur in *Salmonella* enteritis

The causative organism can be isolated in most cases from stool cultures using feces emulsified in saline solution A better technique for obtaining cultures is to swab the rectal mucosa Preliminary incubation in a medium such as selenite F is helpful but cultures can be streaked directly onto SS or desoxycholate citrate agar plates A positive diagnosis should be obtained in at least 80 per cent of cases of bacillary dysentery

Serologic changes are not diagnostic because of the many cross reactions within the *Shigella* group and with other enteric bacilli

Diagnosis *Shigella* infection should be suspected in every febrile diarrheal illness especially if it occurs in epidemic form Outbreaks of staphylococcal food poisoning or *Salmonella* gastroenteritis are usually more explosive than those of bacillary dysentery Staphylococcal food poisoning is usually an afebrile disease in which nausea and vomiting are very severe *Salmonella* infection can be differentiated with certainty only by bacteriologic studies Amebic colitis is rarely epidemic its onset is not usually abrupt and prostrating and motile amebas are found in the stools Diarrheas of viral origin are usually unaccompanied by mucus and blood in the stools but this is not invariable (see p 1105)

In children the onset of otitis tonsillitis pneumonia poliomyelitis or osteomyelitis is often accompanied by diarrhea but careful clinical examination usually clarifies the situation

Treatment The sulfonamides are highly effective in *Shigella* infections Sulfadiazine 4 Gm initially

followed by 1 Gm every 4 to 6 hr is adequate Fluid intake is very important in patients with diarrhea given sulfonamides Poorly absorbed drugs such as Sulfasuxidine (3 to 4 Gm every 6 hr) are effective but offer no advantage Treatment should be continued for 7 to 10 days Occasional strains of *Shigella* are resistant to sulfonamides Oral chloramphenicol and tetracyclines are effective in a dosage of 1 to 2 Gm daily Streptomycin and polymyxin B have been used in a dosage of 0 5 to 1 0 Gm daily by the oral route with good success

Fluid replacement sufficient to maintain urine output of 1 000 ml per day is important intravenous infusion is sometimes needed and rarely blood transfusion is required because of excessive blood loss

The diet is unimportant In many patients symptoms are aggravated by ingestion of food or fluid and it is advisable to rely on the parenteral route during the acute phase of the disease Paregoric codeine or morphine often alleviates abdominal cramping diarrhea and tenesmus

Chloromycetin is more effective in eliminating *Shigella* from the stools of chronic carriers than are the sulfonamides

Prevention The most important prophylactic measures are the maintenance of proper sanitation and adequate sewage disposal The detection and elimination of carriers is difficult and rarely practicable Various vaccines oral and parenteral have been used Although the results of limited trials have been reported with enthusiasm more extensive experience offers no indication that parenteral vaccine exerts a significant protective effect The wide range of potentially pathogenic species necessitating a polyvalent vaccine is another discouraging aspect of this approach to prophylaxis

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124 CHOLERA

W Elizabeth Gambrell

Definition Cholera is an acute infectious disease caused by a spirillum the *Vibrio comma* localized in the gastrointestinal tract and characterized by diarrhea vomiting and extreme dehydration

Etiology The causative agent is a comma shaped gram negative bacillus with a single polar flagellum It is actively motile aerobic and easily stained by the acridine dyes Antigenically there is a single flagellar antigen the H antigen one common somatic or O antigen and several secondary somatic antigens by which different serologic strains can be distinguished

Epidemiology The original home of cholera is the delta of the Ganges where it has occurred year after year for centuries It has not been a problem in the United States since the epidemic of 1873 but it is still endemic and often epidemic in India China and other countries of the Orient The great epidemics of the nineteenth century spread to all but the coldest parts of the world The potential distribution of cholera is practically world wide and in the Far East the danger of epidemics is always present

The organism may persist in nature for a short period of time but is usually spread from person to person by patients in the incubation or convalescent stages or by those with subclinical infections True carriers probably do not exist but convalescent patients may remain carriers for a short period of time The organisms are transmitted in food drink or other material contaminated by infected feces Contaminated water and flies are the principal vehicles Diet which is largely vegetarian and previous enteric infections predispose individuals to cholera The disease cannot spread however when sanitary facilities are in efficient operation

Manifestations There is great difference in the susceptibility of individuals who contract the disease some show acute reactions while others have mild attacks characterized by only slight malaise and diarrhea The incubation period is usually 1 to 3 days followed by a sudden onset In the usual clinical course profuse watery stools occur which are voluminous and frequent and lack all fecal characteristics They are generally light gray (rice water) and contain small flecks of mucus but no pus Tenesmus does not occur Vomiting is copious and may be projectile without nausea or

retching With the tremendous loss of fluid dehydration and hypochloremia become severe and prostration is marked Generalized muscular cramps may cause severe pain Patients remain mentally clear but are extremely apathetic The circulation is markedly affected and peripheral collapse develops rapidly Renal failure with anuria and uremia occurs in severe cases The skin temperature may be subnormal while the rectal temperature is elevated In some cases high temperature results when complications develop such as pneumonia The disease runs its course in 3 to 5 days In properly treated cases the fatality rate is low but during epidemics among inadequately treated patients or those in debilitated states previous to the onset 50 to 70 per cent may die These estimates do not include the milder cases which escape notice

Laboratory Findings The rapid dehydration leads to hemoconcentration and the specific gravity of the blood may rise to 1 070 Large amounts of mineral metabolites are lost especially chloride sodium and calcium and acidosis results

Pathology The pathologic picture is unique in its simplicity as the effects of the infection resemble the results of an overdose of a drastic purgative or of severe food poisoning The gross changes in the intestine result from dehydration which causes pallor and some swelling of the Peyer s patches The cholera vibrios when killed liberate an endotoxin which acts as a severe intestinal irritant and causes denudation of the intestinal epithelium Diarrhea results from the increased permeability of the intestinal mucosa with outpouring of tremendous amounts of fluid Fatalities apparently result from dehydration with the loss of salts and the rapid development of azotemia The organisms live in the intestinal lumen and rarely penetrate the wall Whether the endotoxin has more general effects particularly on the kidney or whether the impairment of renal function is due solely to dehydration and ischemia is controversial

Differential Diagnosis Diagnosis of cholera in areas where the disease is known to be endemic is usually made on clinical findings It is essential to recognize the mild ambulatory cases which are *important potential carriers In an epidemic every* person with any type of gastrointestinal disturbance should be suspected of having cholera until it is proved otherwise The diseases often confused with cholera are acute bacillary dysentery in which the appearance of the stools is different tenesmus is present and collapse is rare in adults *Salmonella* food poisoning which is usually accompanied by nausea and retching with vomiting clinical forms of malaria in which intestinal symptoms with collapse occur heat exhaustion and other conditions leading to a state of shock

The specific diagnosis is based on bacteriologic identification of *V comma* from stool cultures or rectal swabs Smears of feces stained with diluted carbolfuchsin and showing comma forms with the fish in stream appearance are suggestive Cultures from stools in alkaline peptone water usually show the typical organisms concentrated at the surface in 6 hr Suspected colonies from streaks of nutrient agar may be tested with specific *V comma*-agglutinating serum by means of a slide technique

Treatment The natural course of the disease is short and the infection is self limited There is no evidence that the mortality rate is reduced by any of the sulfonamides or antibiotics The tetracycline drugs cause the stools to become negative in 2 or 3 days but do not alter the course of the disease Chloramphenicol has been used orally and intravenously with little effect The real emergency in treatment is to replace the enormous losses of water sodium and potassium The reduction of plasma volume leads to a lowering of blood pressure oliguria anuria and collapse The increased viscosity of the blood with increased erythrocyte mass prevents maintenance of proper circulation Patients who are not comatose or in shock usually recover with oral administration of 1 per cent sodium carbonate normal saline or 1/6 M sodium lactate solution in 50 to 100 ml amounts every half hour until 3 to 5 liters per day have been ingested

Patients who are comatose or in shock should be given intravenous infusions of normal saline or Ringer s lactate solution at the rate of 60 to 100 ml per min receiving 2 liters every 6 to 8 hr for the first 2 days The specific gravity of the blood or hemoglobin or hematocrit determinations may be used as a guide for the amount of fluid necessary Supplementary solutions containing potassium chloride are necessary during the first day of treatment 8 to 16 Gm should be administered over a 24 hr period Patients with severe abdominal cramps may require morphine Atropine by hypodermic or tincture of belladonna orally will decrease the number of stools Nourishment by mouth can be resumed gradually as the gastrointestinal symptoms subside

Prevention Cholera occurs where sanitary safeguards are ineffective Particular emphasis should be placed on proper water supply and food handling All cases and suspected carriers must be isolated Fly control by adequate screening of kitchens wards and latrines is important and destruction of flies and larvae by DDT sprays is effective

Cholera vaccine is employed and will give protection for 6 to 12 months but its value is definitely secondary to proper sanitation

Chloramphenicol and the tetracycline drugs are

more effective against the cholera organism in vitro than the sulfonamides and in patients will cause the organisms to disappear from fecal material in 2 days They may be used to prevent infections from known carriers and convalescent patients

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Section 5 Other Gram-negative Bacillary Infections

125 HEMOPHILUS INFECTIONS

Louis Weinstein

The genus *Hemophilus* consists of nonmotile gram negative rods or coccobacilli which require specific growth factors (X and V) for multiplication The organisms of importance in human disease are *H influenzae H pertussis H ducreyi* the Koch Weeks bacillus and *Moraxella lacunata* Two other species are found in the pharynx of normal individuals and rarely may produce pharyngitis (*H hemolyticus*) or endocarditis (*H parainfluenzae*) The site invaded most frequently is the respiratory tract and the organisms responsible for the bulk of infections are *H influenzae* and *H pertussis*

HEMOPHILUS INFLUENZAE INFECTIONS

Hemophilus influenzae produces a wide variety of diseases in many organ systems The organism was first isolated by Pfeiffer during a pandemic of influenza in 1890 and was thought to be the causative agent of this disease During the 1918 influenza pandemic extensive bacteriologic investigations revealed a high incidence of *H influenzae* in the nasopharynx and lungs of patients in many parts of the world

Etiology *Hemophilus influenzae* is a gram negative nonsporulating pleomorphic rod In exudates the organisms are usually predominantly coccobacillary and can be mistaken for pneumococci or meningococci Some strains demonstrate bipolar staining and bacillary forms that vary from short rods to long filamentous ones occur The pleomorphism of the organism is its most striking feature

Hemophilus influenzae grows well on chocolate agar and Levinthal's medium which has the advantage of being transparent On Levinthal's agar typical colonies are iridescent when viewed by obliquely transmitted light when they are about 4 to 6 hr old this property disappears after 24 hr

Virulent strains of the influenza bacillus are encapsulated Although it had been thought that strains without capsules were nonpathogenic recent observations have implicated such strains in infections of the respiratory tract On the basis of specific capsular polysaccharides *H influenzae* may be classified into six types Type B produces about 95 per cent of human infections Three of the types are immunologically related to certain pneumococci Influenza bacilli lack certain enzyme systems common to most bacterial species and very little fermentation of carbohydrates takes place Like pneumococci this organism is soluble in bile

Epidemiology *Hemophilus influenzae* infects only man naturally It is not ordinarily invasive for any of the smaller animals although monkeys can be infected experimentally Although the pathogenicity of the influenza bacillus is closely related to the presence of the capsule nonencapsulated strains can also produce disease

The incidence of *H influenzae* infections is greatest in the winter and early spring Nose and throat cultures during these seasons reveal encapsulated or nonencapsulated strains in many asymptomatic individuals Penicillin therapy increases the incidence of positive throat cultures in a population

Children in the first 2 months of life have a high level of bactericidal antibody for *H influenzae* passively transferred from the mother Between the ages of two months and three years most children

show little serum bactericidal capacity but with aging the number of individuals whose blood exerts a lethal action against the organism increases

The influenza bacillus is transmitted by way of the respiratory tract from carriers or active cases of infection

Pathology The characteristic tissue response produced by *H influenzae* is acute suppurative inflammation Infections of the larynx trachea and bronchial tree are characterized by inflammation and edema of the mucosa and the presence of thick exudate and invasion of the lungs results in a bronchopneumonia similar to that produced by other bacteria Swelling of the small radicles of the bronchial tree is common and particularly in young children a severe diffuse bronchiolitis can occur In influenzal meningitis the vertex of the brain is covered with thick greenish yellow exudate

Microscopic examination of the lesions produced by *H influenzae* reveals an exudate consisting primarily of polymorphonuclear leukocytes and large numbers of organisms enmeshed in fibrin

Clinical Manifestations Infections due to *H influenzae* are usually accompanied by a constitutional reaction In severe disease there is high fever usually without rigors and generalized malaise In milder infections systemic manifestations are slight and fever is inconstant

The most important manifestations of influenzal infection result from disturbances at the primary sites of bacterial multiplication The commonest diseases produced by *H influenzae* are pharyngitis epiglottitis laryngotracheitis pneumonia bronchitis and bronchiolitis otitis media and meningitis The symptoms and signs of influenzal invasion of the respiratory tract or meninges are similar to those of infection of these areas by other organisms and differential etiologic diagnosis depends upon epidemiologic background the age of the patient and demonstration of the causative agent

Pharyngitis *Hemophilus influenzae* is a relatively common cause of pharyngitis in children and acute influenzal pharyngitis is being observed with increasing frequency in adults where it often occurs as a complication of the chemotherapy of other infections Examination of the throat usually reveals only marked redness and injection Very rarely patches of soft yellow exudate may be present The pharyngitis tends to persist for many days unless properly treated Discomfort in the pharynx is often out of proportion to the physical findings

Epiglottitis Disease of the upper respiratory tract produced by *H influenzae* is sometimes limited to the epiglottis which becomes reddened swollen and stiff Discomfort in the hypopharynx and "croupy breathing may progress to a point at which tracheotomy becomes necessary This disease is rare in adults

Laryngotracheobronchitis The entire laryngotracheobronchial tree may be the site of infection, with resulting rapidly progressive obstruction of the airway Croupy cough is accompanied by increasing signs of respiratory embarrassment and tracheotomy is sometimes necessary Influenzal laryngotracheitis is very rare in adults The disease can lead to death within 18 to 24 hr

Pneumonia Primary pneumonia due to *H influenzae* with rare exceptions is a disease of children. In the adult it is usually secondary to viral influenza measles or bacterial pneumonitis It may complicate rubeola or pertussis in the young Bacteremia occurs in approximately one third of the cases

Bronchitis and Bronchiolitis Severe diffuse bronchiolitis characterized by persistent nonproductive cough wheezing and dyspnea occurs in children Physical examination usually reveals lowering and fixation of the diaphragms prolonged expirations and typically asthmatic breathing Roentgenographic examination of the chest reveals increased radiolucence and flattening of the diaphragms consistent with emphysema This is an extremely serious illness and unless promptly recognized and treated may be rapidly fatal

Otitis Media *Hemophilus influenzae* is a common cause of suppurative otitis media in children the infection is uncommon in adults Influenzal middle ear disease is indistinguishable on clinical grounds from infection due to other bacteria

Meningitis The influenza bacillus is the commonest cause of meningitis between the ages of six months and two years and is frequent in later childhood In adults it may follow operation on or injury to the head The writer has studied one adult in whom spinal anesthesia in the presence of a severe sore throat was followed within 24 hr by meningitis due to type B *H influenzae* Ninety five per cent of cases are produced by type B organisms a few by type A and a rare one by nonencapsulated strains About two thirds of the patients have a preceding infection of the upper respiratory tract and about one third have bronchopneumonia Signs of meningeal irritation stiff neck and back and positive Kernig and Brudzinski signs are usually prominent except in very young babies in whom bulging of the fontanelles may be the only sign The diagnosis should be suspected because of the age of the patient and the frequent prodrome of respiratory infection it is confirmed by identification of the organisms from the spinal fluid or blood

Other Diseases Subacute and acute bacterial endocarditis may be produced by *H influenzae*

although more infections of the heart valves have been due to *H parainfluenzae* The influenza bacillus is a rare cause of suppurative *pericarditis* In the winter *acute conjunctivitis* may be due to *H influenzae* While there are no clinical features which distinguish this from "pink eye" produced by the Koch Weeks bacillus epidemics of conjunctivitis due to the latter are most common in the summer Although it has been suggested that *H influenzae* and the Koch Weeks bacillus are identical more recent observation has indicated that although they are antigenically related they are distinct species *Moraxella lacunata* is also an occasional cause of acute purulent conjunctivitis Acute pyogenic *arthritis* due to *H influenzae* has been reported One of the very important lesions in which this organism plays a role in the adult is *bronchiectasis* Together with other pyogenic bacteria it can be responsible for the perpetuation of this disease

Laboratory Findings As a rule infections due to *H influenzae* are accompanied by polymorphonuclear leukocytosis ranging from 15 000 to 30 000 per cubic millimeter In young children with severe disease leukopenia (2 000 to 3 000 leukocytes per cubic millimeter) with a deficiency of polymorphonuclear leukocytes can occur Bacteremia is of irregular occurrence in influenzal infections of the respiratory tract but is demonstrable in about 50 per cent of cases of meningitis

Course and Complications The course of *H influenzae* infections is influenced completely by the location of the disease Epiglottitis laryngotracheobronchitis bronchiolitis or pneumonia may be fulminating particularly in young children Some of these patients succumb to the uncontrolled infection but in many the cause of death is obstruction of the airway This cannot always be relieved by surgical methods because impediment to flow of air is most marked in the smaller radicles of the bronchial tree Virtually 100 per cent of untreated cases of influenzal meningitis terminate fatally Internal and external hydrocephalus brain abscess subdural empyema diffuse cortical necrosis and shock (the Waterhouse-Friderichsen syndrome) are possible complications With specific therapy the incidence of complications is generally sharply reduced However if subdural aspiration is carried out routinely in children with influenzal meningitis which is responding to antibiotics sterile fluid is demonstrable in about half the cases Neurologic disturbances from subdural effusions are uncommon Epileptiform seizures can occur while the disease is responding favorably to chemotherapy

Treatment Specific serotherapy is presently used only in unusual situations The sulfonamides streptomycin the tetracyclines and chloramphenicol inhibit *H influenzae* Streptomycin is very effective but has the disadvantage of leading to the rapid development of bacterial resistance Sulfadiazine or sulfisoxazole (Gantrisin) is effective in influenzal pharyngitis but the tetracycline compounds are more active than the sulfonamides and are preferred for the therapy of lesions involving the respiratory tract There is controversy concerning the treatment of influenzal bacterial meningitis but several facts are clear The sulfonamides should never be used alone Streptomycin given both intramuscularly and intraspinally reduces the mortality rate but about 10 per cent of patients develop drug resistant organisms 48 to 72 hr after initiation of treatment The tetracyclines alone do not eradicate the meningeal infection Chloramphenicol (50 to 75 mg per kg body weight per day) and sulfadiazine (0 1 Gm per lb body weight per day the initial dose being one half the quantity required daily) constitute the preferred regimen in many clinics Death or complications still occur and clearing of the organisms from the spinal fluid may be delayed In the writer's experience the most effective therapy is as follows Streptomycin (no more than 25 mg in children under age three and 50 mg in older ones) diluted in 10 ml saline is injected intraspinally at the time the diagnosis is established and once again 12 hr later the drug is not administered intraspinally after the second dose Streptomycin (0 5 to 1 0 Gm daily in divided doses depending on the age and size of the patient) is given intramuscularly and sulfadiazine or sulfisoxazole (Gantrisin) is administered in quantities sufficient to produce a blood level of 12 to 15 mg per 100 ml Treatment is continued for 2 weeks In 40 consecutive cases of influenzal meningitis so treated there have been no deaths and no detectable complications

PERTUSSIS

Whooping cough is a common disease which affects about 65 per cent of all unimmunized children It is characterized by an inflammatory reaction involving the entire respiratory tract which produces paroxysmal cough and the typical inspiratory stridor or "whoop"

Etiology The causative agent is *Hemophilus pertussis* a short or ovoid gram negative nonmotile nonsporulating facultatively anaerobic bacillus It shows very little tendency towards pleomorphism Bipolar staining is frequent and encapsulation can be demonstrated by special stains

The pertussis bacillus requires both the X and V factors for growth especially for initial isolation and multiplies best on Bordet Gengou medium

Hemophilus pertussis is a uniform antigenic species without fixed variation or types

The pertussis bacillus produces no demonstrable endotoxin although it has been postulated that some of the clinical features of whooping cough may be due to such material definite evidence for this is lacking

Epidemiology Pertussis is world wide and may be endemic or epidemic If the disease has not been present for several years it tends to assume epidemic proportions when it reappears In some geographic locations the disease is most common during the winter and in others it is seen with greatest frequency in the late summer and fall The index of contagion is 80 to 100 per cent about 200 000 cases occur in the United States each year

Approximately 40 per cent of cases of pertussis occur in the first two years of life the same number is observed between two and five years At least 50 per cent of all children have had whooping cough before they reach the age of five and 75 per cent by the age of seventeen

Pertussis is spread by droplets from the respiratory tract It has been suggested that rarely the organisms may be transmitted by fomites The infectivity of the disease during the incubation period is questionable it is most contagious during the catarrhal stage Healthy carriers play no role in dissemination mild or missed cases are of great importance The duration of contagiousness is about 4 to 6 weeks

Pathology The initial lesion in whooping cough is hyperplasia of the peribronchial lymphoid tissue and tracheobronchial lymph nodes Subsequently or perhaps coincidentally the bronchi trachea larynx and nasopharynx are involved in a necrotizing inflammatory reaction The organisms are present in large numbers between the cilia of the epithelial cells lining the trachea and bronchi It has been thought that the pulmonary alveoli are not involved in pertussis but there is often a diffuse bronchopneumonia with marked desquamation of the alveolar epithelium and lymphocytic infiltration of the peribronchial tissues and alveolar walls

Clinical Manifestations The incubation period of whooping cough averages 12 to 15 days although it can be as long as 20 days The first clinical manifestations are nonspecific consisting of slight nasal discharge conjunctivitis and mild cough without fever This *catarrhal stage* lasts for 7 to 14 days

The *paroxysmal phase* of pertussis follows the *catarrhal stage* and is characterized by paroxysms of coughing ending in a loud crowing inspiratory noise (the whoop) the expulsion of varying quantities of thick mucoid sputum from the respiratory tract and vomiting Episodes of cough may be as few as 1 or 2 or as many as 40 to 50 per day Children under the age of six months frequently do not whoop The mere presence of a whoop is in itself not diagnostic of pertussis Rarely the paroxysms of coughing and whooping are replaced completely by sneezing

Fever of appreciable degree does not occur in the paroxysmal phase of pertussis unless complications are present Vomiting frequently follows spells of coughing but is not a specific manifestation of the disease Soreness over the trachea and main bronchi are common Spasm ulcer and more rarely edema of the glottis sometimes occur In cases with severe vomiting and inability to retain food serious inanition wasting and tetany may appear

There is a bleeding tendency in pertussis This has been attributed to the effect of an angiotoxin (not proved) elaborated by the organism which increases the ease of rupture of blood vessel walls. Hemoptysis epistaxis purpura and subconjunctival or intestinal hemorrhages may occur but are usually of little clinical significance

Physical examination in pertussis is often entirely normal There may be redness and injection of the blood vessels of the nose and pharynx Although there are usually no abnormal findings in the lungs fine crackling "sticky" rales are sometimes present. There are ulcers of the frenum of the tongue in about 20 per cent of cases these occur only when the lower central incisor teeth are present

The paroxysmal stage of pertussis usually lasts from 1 to 6 weeks When coughing persists beyond 6 weeks it is usually due to the development of a so called habit whoop and not to continuation of the disease

Laboratory Findings The peripheral white blood count is as a rule elevated in pertussis The total count may be over 100 000 per cubic millimeter and lymphocytes may constitute 90 per cent of the cells All the lymphocytes are mature This helps to distinguish the blood picture from that of acute leukemia but not from acute lymphocytosis Blood cultures are sterile Cultures of the upper part of the nasopharynx reveal *H pertussis* the incidence of positive isolations varying with the stage of the disease X ray study of the lungs in the uncomplicated case usually reveals only hilar lymphadenopathy and increase in the density of the bronchovascular markings

Complications Bronchopneumonia occurs in from 1 to 10 per cent of cases the organisms most frequently involved are the beta hemolytic *Streptococcus Diplococcus pneumoniae Staphylococcus aureus H influenzae* and *H pertussis* When pneumonitis appears during the course of chemotherapy the bacteria most often responsible are *Escherichia coli Proteus* strains *Aerobacter aerogenes* or *Pseudomonas aeruginosa* Another impor

tant complication is atelectasis small areas of collapse are an almost constant finding in this infection but major portions or even a whole lung may be involved Pneumothorax is rare

The severe coughing of pertussis may lead to several complications Hemorrhage may appear in the anterior chamber of the eye or in the retina Detachment of the retina and blindness develop in rare cases Prolapse of the rectum and inguinal or umbilical hernias have been noted Otitis media is observed in about 10 per cent of cases the organisms most frequently involved are the beta hemolytic *Streptococcus* and *S aureus* although *H pertussis* is sometimes responsible

Nervous system manifestations are not rare in pertussis The commonest is convulsions they often come with the sudden fever of secondary bacterial infection Other causes of seizures are encephalopathy (1 to 14 per cent of cases) multiple petechial or gross hemorrhages of the brain and cerebral hypoxia due to the combined effect of anoxic anoxia and venous stasis in the brain The encephalopathy is characterized by an increase in the protein and cell content of the spinal fluid Its etiology is unknown Hyperreflexia nuchal rigidity cranial nerve palsies areflexia extensor plantar responses flaccid hemiplegia spasticity of the extremities opisthotonos difficulty in speaking twitching papilledema nystagmus blindness strabismus and difficulty in swallowing can all occur Some of the more important residua are mental retardation recurrent convulsions behavior and personality disorders amnesia aphasia diffuse cerebral atrophy chorea athetosis hydrocephalus epilepsy and idiocy

Diagnosis The diagnosis of pertussis can frequently be made on clinical grounds alone A known contact is helpful but the appearance of paroxysms of typical coughing and whooping after a short period of an undefined upper respiratory tract infection is strongly suggestive It must be stressed however that in babies under the age of six months there is usually only paroxysmal coughing without the characteristic whoop

An increased white blood count with a large increase in lymphocytes is characteristic the lymphocyte count must however be evaluated in relation to the age of the patient

Isolation of *H pertussis* from the respiratory tract establishes the diagnosis unfortunately this is not possible in many cases Using cough plates and nasopharyngeal swabs positive cultures can be obtained in 90 per cent of patients in the catarrhal stage of the disease pertussis however is rarely seen by the physician in this phase The incidence of positive cultures is lower after paroxysmal coughing appears and decreases with the duration of symptoms

Serologic studies are of little or no help in establishing the presence of pertussis

Prevention Active immunization is effective in preventing pertussis in the majority of individuals who are given vaccine Immunization may be started at the age of three months both antibody production and protection against invasion by *H pertussis* result If the procedure is carried out at this early age a "booster" injection should be administered at the end of the first year of life and again just before the child starts to school Although it is not commonly practiced passive immunity can be conferred on the newborn child by active immunization of the mother beginning in the sixth or seventh month of pregnancy Vaccine should not be given in the presence of the active disease not only is it useless but it may provoke serious neurologic reactions

In children who have been exposed to a case of pertussis but have not been actively immunized passive protection may be given by the injection of 20 to 30 ml human hyperimmune pertussis antiserum or 2 ml immune gamma globulin as soon as possible after exposure and again 1 week later Such prophylaxis is 75 to 85 per cent effective

Treatment Although most of the antimicrobial drugs have been employed in the treatment of pertussis there is no incontrovertible evidence that they are strikingly beneficial Aureomycin (chlortetracycline) chloramphenicol Terramycin (oxytetracycline) and erythromycin have been used but the results obtained in controlled studies are not remarkable

There are few controlled studies of serum therapy in whooping cough but in many clinics it is the practice to administer human hyperimmune serum (20 ml every 48 hr for 3 doses) or immune gamma globulin (2 ml every 48 hr for 3 doses) to all children with pertussis under the age of two years

Most important in the program of therapy is repair of the water and salt loss which follows severe and frequent vomiting If failure to retain food is combatted by prompt refeeding whooping cough patients can be made to maintain or gain weight

Early detection and treatment of complications is one of the most important factors in the reduction of mortality in pertussis The prompt recognition of secondary bacterial infections of the lungs or middle ear and therapy with a properly selected antibiotic agent lead to cure in practically all cases When gross atelectasis occurs correction by tracheal catheter suction or bronchoscopy may be lifesaving Little can be done to influence the course or outcome of such complications as gross cerebral hemorrhage or encephalopathy

Proper management of whooping cough has made

the outlook for complete recovery excellent There have been only two fatalities in 500 patients with this infection in the last 8 years in the writer's clinic neither was due to a preventable or treatable complication

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126 CHANCROID

Albert Heyman

Definition Chancroid is an acute localized venereal disease caused by the Ducrey bacillus It is characterized by ulceration at the site of inoculation and by enlargement and suppuration of the regional lymph nodes

Etiology The etiologic agent of chancroid the Ducrey bacillus is a short plump gram negative organism with rounded ends When stained by special methods the bacillus exhibits bipolar staining In the stained smears of genital lesions the organisms usually appear singly or in small clusters but they may be arranged in long parallel columns between cells or shreds of mucus Occasionally the bacilli are situated intracellularly The organism can be cultivated in whole defibrinated blood or nutrient broth containing blood When grown in pure culture in a liquid medium the Ducrey bacillus appears in long tangled chains composed of both coccal and bacillary forms

Incidence The number of cases of chancroid occurring every year cannot be determined satisfactorily since accurate diagnosis of this condition is not generally attempted A diagnosis of chancroid is frequently applied to genital lesions improving with sulfonamide therapy in which the *Treponema pallidum* cannot be demonstrated The disease is encountered in the West Indies North Africa and the Orient particularly in the lower economic groups of the population It is also prevalent in the Southeastern part of the United States and is more frequent in Negroes than in whites Approximately 2 900 cases were reported in the United States in 1955 the true incidence is probably considerably higher

Pathogenesis Chancroid is usually contracted by sexual intercourse and the lesions are almost always located about the genitalia The disease can apparently be acquired from sexual partners who show no evidence of an active chancroidal infection The organism has been cultivated from the smegma and vaginal secretions in patients without clinical manifestations of the disease Such individuals may be carriers of the Ducrey bacillus The organism readily produces an infection when inoculated into open or slightly abraded areas of the skin or mucous membranes Chancroidal ulcerations frequently occur in areas of the genitalia where minor abrasions may be present (fourchette of the vulva edge of phimotic prepuce and frenum) After an incubation period of 2 to 5 days a localized ulceration appears at the site of inoculation This may be followed later by inflammation and suppuration of the regional lymph nodes

Chancroidal infection produces a distinct histologic appearance The base of the ulcer is a shallow zone made up of polymorphonuclear leukocytes fibrin red blood cells and necrotic tissue Below this is a fairly wide layer consisting chiefly of proliferating endothelial cells and newly formed blood vessels some of which show degeneration of their

walls Finally there is a deep zone in which a dense infiltration of plasma cells and lymphocytes occurs This histologic pattern is sufficiently characteristic to permit differentiation from other genital lesions Biopsy is a valuable diagnostic procedure

Clinical Manifestations The typical chancroidal lesion is a painful shallow irregular ulcer with ragged undermined edges a granular friable base and a dirty yellow exudate The lesion is characteristically nonindurated and for this reason has been called *soft chancre* The size of the ulceration varies but seldom exceeds 2 cm in diameter Multiple lesions resemble a folliculitis or pyogenic infection Almost any portion of the genitalia may be involved but extragenital lesions are rare In about 50 per cent of the patients inflammation and suppuration of the inguinal lymph nodes will occur The term *bubo* is given to this type of lymphadenitis The chancroidal bubo develops rapidly and becomes a very painful inflammatory inguinal mass When suppuration occurs the mass may become tensely fluctuant and may rupture spontaneously leaving a large single craterlike abscess Mild constitutional symptoms may accompany the involvement of the inguinal lymph nodes and the patient may complain of headache malaise fever or anorexia

Diagnosis Although the clinical appearance of chancroid is often sufficiently characteristic to suggest the correct diagnosis laboratory confirmation is desirable Stained smears or culture of the exudate taken from the undermined edge of the lesion will reveal the Ducrey bacillus in the majority of the early cases The organism is not easily demonstrated however in larger lesions when secondary bacterial contamination has occurred Biopsy is feasible in such cases and is an efficient method of diagnosis Attempts to demonstrate the organism in the buboes by either culture or smear usually are not successful The majority of patients with chancroidal infection will exhibit a positive skin reaction to an intradermal injection of killed Ducrey bacilli The value of this skin test is limited by the fact that a positive reaction persists for years after exposure to the infection One cannot be certain therefore whether a positive skin test in an individual patient represents the existing chancroidal infection or a previous one Early syphilis may be present concurrently with chancroid in these patients Serologic tests and dark field examination of the lesions and regional lymph nodes should be done to rule out this possibility

Treatment Sulfadiazine or Gantrisin is the drug of choice in the treatment of chancroid doses of 4 Gm a day for 7 to 12 days are usually curative Local medication is not necessary but saline soaks and cleanliness are advised Although the buboes usually subside with sulfonamide therapy fluctuation may persist and the node should be aspirated in order to prevent spontaneous rupture Streptomycin chloramphenicol, and the tetracyclines in doses of 2 Gm a day for 7 to 10 days will each produce satisfactory healing of the lesions of chancroid The use of these agents is rarely necessary since sulfadiazine is equally effective The antibiotics with treponemicidal properties should not be used in the treatment of chancroid until repeated dark field examination and serologic tests have ruled out the possibility of early syphilis

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127 BRUCELLOSIS (Undulant Fever)

Wesley W Spink

Definition Brucellosis is an infectious disease due to microorganisms belonging to the genus *Brucella* and is transmitted to man from lower animals The acute form of the illness is frequently characterized by a febrile illness without localizing findings while the chronic form is featured by fever weakness and vague complaints which may persist for months and years

History Accurate clinical descriptions of brucellosis have been ascribed to Hippocrates but the first clear cut picture of the disease was presented in 1863 by Marston who as a British Army surgeon in Malta detailed his own case and those of others The etiologic agent was discovered by Bruce in 1886 The outstanding clinical description of the disease is contained in the monograph by Hughes published in 1897 Wright and Semple in 1897 demonstrated agglutinins for *Brucella* in human blood In the same year Bang reported that *Bacillus abortus* was the cause of contagious abortion in cattle in Denmark The Mediterranean Fever Commission Reports of 1905 to 1907 detail the classic studies on epidemiology The first recognized human case of brucellosis in the United States occurred in a nurse in Washington D C and was described by Craig in 1906 In 1911 brucellosis was found to be endemic in the goats of Texas and Gentry and Ferenbaugh traced human cases to this source Traum first identified *Brucella* from aborting sows in 1914 and Evans in 1918 distinguished the difference between *Brucella melitensis* and *Brucella abortus* and suggested that raw milk

from infected cows could be the source of human cases In 1924 Keefer described the first human case of brucellosis in this country due to organisms other than *Br melitensis*

Etiology Human brucellosis is due to one of three species of *Brucella*—viz *Br melitensis* (goats) *Br suis* (hogs) and *Br abortus* (cattle) *Brucella* are small nonmotile non spore forming rods staining gram negative Growth is best supported at 37 C in trypticase soy broth or tryptose phosphate broth having a pH of 6 6 to 6 8 The primary isolation of *Br abortus* requires displacement of 10 per cent of the air by carbon dioxide The differentiation of the three species is dependent upon biochemical and serologic reaction In general *Br melitensis* is the most invasive of the three species which fact is reflected in the severity of human infections while *Br abortus* is the least virulent

Epidemiology The natural reservoir of brucellosis is in domestic animals particularly cattle swine goats and sheep The disease is very rarely transmitted from human to human By and large man acquires brucellosis through the ingestion of milk or milk products containing viable *Brucella* or through contact of the skin with infected tissues excretions and secretions Recent epidemiologic studies in the United States indicate that the majority of cases are acquired through contact and fewer and fewer cases are caused by the ingestion of milk This trend is due to the enactment of local and state ordinances requiring all milk sold for human consumption to be pasteurized There is some evidence that brucellosis may be air borne with the disease resulting from the inhalation of *Brucella* Infections caused by *Br abortus* are spread through cow s milk or through dermal contact with *Brucella* Epidemics of brucellosis traced to raw cow s milk have been caused by *Br abortus* Contact with infected porcine tissue is a common cause of infections due to *Br suis* While infections due to *Br melitensis* result from eating goat s cheese or drinking unpasteurized goat s milk studies in Minnesota and Iowa have shown that contact with infected hogs has been the source of *melitensis* infections It is readily appreciated why brucellosis is primarily a disease of rural areas and why it is considered an occupational disease involving meat packing plant employees farmers veterinarians and livestock producers

Pathogenesis Following invasion of the body by *Brucella* through the oropharynx or through the skin the organisms tend to localize in tissues of the reticuloendothelial system such as the bone marrow lymph nodes liver spleen and also the kidneys A characteristic but nonspecific reaction of these tissues to the *Brucella* is the appearance of epithelioid cells giant cells of the foreign body and Langhans types and lymphocytes and plasma cells Necrosis and caseation rarely occur in these granulomatous areas When caseation is encountered it is usually caused by *Br suis* The granulomas are similar to those of sarcoidosis and tuberculosis Other less frequent sites of localization of *Brucella* are the bones especially the spine the endocardium and the testes While the central nervous system and peripheral nerves are commonly affected deleteriously by *Brucella* the mechanism whereby this takes place is not known Like other blood borne infections *Brucella* may on occasion localize in any tissue or organ in the body Though brucellosis is a common cause of abortions in cattle swine and goats authentic cases of human abortions occur no more frequently in this disease than in other bacteremias Orchitis in the male is rarely the cause of subsequent sterility

Manifestations The incubation period varies between 5 and 21 days though many months may elapse between the time of infection and the first appearance of symptoms The onset in many instances may be insidious the patients exhibiting a low grade fever with no localizing findings and complaining of headache weakness insomnia, sweats anorexia constipation pain over the spine and generalized aches and pains Less frequently the disease may be ushered in by chills high fever and prostration but again, localizing abnormal physical findings may be absent In general, about 50 per cent of the patients exhibit enlarged lymph nodes especially of the cervical region and splenomegaly is detected in about one third of the cases An enlarged and tender spleen is usually associated with the more severe cases Pain on pressure over the vertebrae occurs occasionally Pain distributed over the course of the peripheral nerves particularly the sciatic nerve is encountered Orchitis appears after several days of illness and like the orchitis of mumps is ushered in with a chill or chilliness high fever and tender and enlarged testes Painful and swollen joints are seen occasionally but persistent and deforming arthritis is not specific for the disease Signs and symptoms referable to the lungs and pleurae are uncommon A rare but serious complication is subacute bacterial endocarditis Ocular disorders are associated with the more chronic forms of the disease

The initial febrile stage of the illness may endure for only a few days or up to several weeks The persistence of fever and symptoms is definitely related to physical activity Rest in bed during the acute illness is frequently associated with prompt improvement The natural course of the disease in the majority of patients is marked by a permanent remission of fever and symptoms within 3 to 6

months A small number of bacteriologically proved cases may have an illness that persists longer than 1 year

The present status of chronic brucellosis is extremely difficult to assess There is no doubt that the infection may persist in some individuals for months and years Such patients exhibit a state of ill health manifested by weakness fatigue mental depression vague aches and pains and no abnormal physical findings Intermittent fever may occur The precise incidence of chronic brucellosis awaits further investigation Much of the data now available is based upon uncritical clinical and laboratory studies

Laboratory Procedures A precise diagnosis of brucellosis is dependent upon the results of laboratory procedures

Blood The total leukocyte count is usually normal or slightly reduced but is rarely over 10 000 cells per cubic millimeter The differential count reveals a relative lymphocytosis The erythrocyte sedimentation rate is of no specific diagnostic aid the rates being normal or accelerated

The most practical method for screening suspected cases of brucellosis is the *agglutination* reaction Agglutinins usually appear during the second or third week of illness If proper techniques and antigen are employed agglutinins are demonstrated in the vast majority of bacteriologically proved cases Active brucellosis is usually associated with titers of 1 100 or above Agglutinins for brucellosis are not always specific since cross reactions occur with the cholera vibrio and with *Pasteurella tularensis* Agglutinins may persist in the blood long after the patient has recovered

At least *one culture* of blood and preferably more should be carried out in every suspected case of brucellosis Cultures of *Brucella* have been isolated from aspirated sternal bone marrow when simultaneous blood cultures remained sterile It is too impractical for routine purposes to attempt to isolate *Brucella* from the urine bile or feces

The *opsonocytophagic test* which is a measure of the phagocytosis of *Brucella* by polymorphonuclear neutrophil leukocytes is of extremely doubtful diagnostic aid The *complement fixation test* does not contribute enough additional information to warrant its use

Intradermal Tests Various antigenic preparations including killed organisms are used widely for diagnostic purposes A positive reaction has no more significance than that obtained with tuberculin in suspected cases of tuberculosis A positive reaction indicates previous invasion of the body by *Brucella* and does not mean that active disease is present Unfortunately many instances of chronic brucellosis are being diagnosed on the basis of a vague illness and positive intradermal tests When agglutinins are absent and cultures remain sterile considerable caution must be exercised before making a diagnosis of brucellosis even though the skin test is positive Negative skin tests are encountered in severe cases of brucellosis where a high titer of agglutinins is present and a bacteremia is demonstrated

In summary the diagnosis of brucellosis depends upon a correlation of epidemiologic data the nature of the illness and laboratory information, such as the presence of agglutinins and isolation of *Brucella* from the tissues or blood

Differential Diagnosis Brucellosis must be differentiated from other acute febrile illnesses such as *influenza* and other *upper respiratory diseases* of doubtful etiology Brucellosis is not commonly associated with coryza or pharyngitis Other diseases from which it must be differentiated include *malaria* and *typhoid fever* Brucellosis may be confused with *infectious mononucleosis* but the characteristic blood picture and the elevated titer of heterophil antibodies in the latter disease are helpful differential aids

Chronic brucellosis simulates *psychoneurosis anxiety states* and *chronic nervous exhaustion* Indeed a patient with brucellosis may suffer from the foregoing nervous disorders Some confusion may arise in differentiating it from other diseases including tuberculosis and lymphoblastoma especially Hodgkin s disease

Treatment Unfortunately much information of a popular nature on brucellosis has been disseminated widely The general public has heard or read that brucellosis is a chronic disease which may last for years and that no satisfactory treatment is available Therefore any physician who believes that he is dealing with a case of brucellosis should reassure the patient that the disease is self limiting and that complete recovery will ensue Psychotherapy is extremely important in the management of these mentally depressed and tired patients The acutely ill and febrile patient should be kept in bed Many patients will recover completely following a period of rest

Over the years the lack of specific treatment for brucellosis has been emphasized by the number of agents and procedures that have been recommended and then discarded one by one Although sulfanilamide and its various derivatives can suppress the growth of brucellae these agents are unsatisfactory for the treatment of human brucellosis Penicillin is an ineffective drug for brucellosis Streptomycin and dihydrostreptomycin are unusual drugs in that they not only inhibit growth of brucellae but they can kill large numbers of the organisms within a relatively short period of time However strepto-

from infected cows could be the source of human cases In 1924 Keefer described the first human case of brucellosis in this country due to organisms other than *Br melitensis*

Etiology Human brucellosis is due to one of three species of *Brucella*—viz *Br melitensis* (goats) *Br suis* (hogs) and *Br abortus* (cattle) *Brucella* are small nonmotile non spore forming rods staining gram negative Growth is best supported at 37 C in trypticase soy broth or tryptose phosphate broth having a pH of 6 6 to 6 8 The primary isolation of *Br abortus* requires displacement of 10 per cent of the air by carbon dioxide The differentiation of the three species is dependent upon biochemical and serologic reaction In general *Br melitensis* is the most invasive of the three species which fact is reflected in the severity of human infections while *Br abortus* is the least virulent

Epidemiology The natural reservoir of brucellosis is in domestic animals particularly cattle swine goats and sheep The disease is very rarely transmitted from human to human By and large man acquires brucellosis through the ingestion of milk or milk products containing viable *Brucella* or through contact of the skin with infected tissues excretions and secretions Recent epidemiologic studies in the United States indicate that the majority of cases are acquired through contact and fewer and fewer cases are caused by the ingestion of milk This trend is due to the enactment of local and state ordinances requiring all milk sold for human consumption to be pasteurized There is some evidence that brucellosis may be air borne with the disease resulting from the inhalation of *Brucella* Infections caused by *Br abortus* are spread through cow s milk or through dermal contact with *Brucella* Epidemics of brucellosis traced to raw cow s milk have been caused by *Br abortus* Contact with infected porcine tissue is a common cause of infections due to *Br suis* While infections due to *Br melitensis* result from eating goat s cheese or drinking unpasteurized goat s milk studies in Minnesota and Iowa have shown that contact with infected hogs has been the source of *melitensis* infections It is readily appreciated why brucellosis is primarily a disease of rural areas and why it is considered an occupational disease involving meat packing plant employees farmers veterinarians and livestock producers

Pathogenesis Following invasion of the body by *Brucella* through the oropharynx or through the skin the organisms tend to localize in tissues of the reticuloendothelial system such as the bone marrow lymph nodes liver spleen and also the kidneys A characteristic but nonspecific reaction of these tissues to the *Brucella* is the appearance of epithelioid cells giant cells of the foreign body and Langhans types and lymphocytes and plasma cells Necrosis and caseation rarely occur in these *granulomatous* areas When caseation is encountered it is usually caused by *Br suis* The granulomas are similar to those of sarcoidosis and tuberculosis Other less frequent sites of localization of *Brucella* are the bones especially the spine the endocardium and the testes While the central nervous system and peripheral nerves are commonly affected deleteriously by *Brucella* the mechanism whereby this takes place is not known Like other blood borne infections *Brucella* may on occasion localize in any tissue or organ in the body Though brucellosis is a common cause of abortions in cattle swine and goats authentic cases of human abortions occur no more frequently in this disease than in other bacteremias Orchitis in the male is rarely the cause of subsequent sterility

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Prevention As long as the reservoir of brucellosis persists in domestic animals human brucellosis will occur The only practical means of eliminating the disease in human beings is to eradicate the disease from cattle hogs sheep and goats Control measures in animals are being worked out in several areas in the United States Since human brucellosis is contracted through the ingestion of contaminated milk and milk products it is essential that only properly pasteurized milk be utilized for human consumption Brucellosis is an occupational disease involving farmers livestock workers veterinarians and those working in packing plants There are no dependable and safe means available for immunizing these groups against the disease

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128 TULAREMIA

Leighton E Cluff and Ivan L Bennett Jr

Definition Tularemia (rabbit fever deer fly fever Ohara s disease) is an infectious disease of animals transmitted to man by direct contact or by insect vectors A cutaneous or mucous membrane lesion at the site of inoculation and regional lymph node enlargement are the characteristic manifestations of the disease in the human being

History The microorganism responsible for tularemia was identified by McCoy and Chapin in 1912 among infected ground squirrels in Tulare County Calif The first description of tularemia in man was that by Wherry and Lamb in 1914

Etiology *Pasteurella tularensis* is a pleomorphic nonsporulating gram negative bacillus It can be cultured only on media containing glucose cystine and serum Thorough cooking renders meat from infected animals safe for consumption but tularemia can develop in persons handling carcasses that have been frozen for many days *Pasteurella tularensis* is related antigenically to the causative organisms of brucellosis and plague and possesses an endotoxin similar to those of many other gram negative bacteria

Epidemiology and Pathogenesis Contact with infected animals is the commonest source of tularemia in man but the disease also may be acquired from insects or by exposure to the organism in the laboratory A variety of rodents carnivores ungulates birds and arthropods are naturally infected by *Past tularensis* including rabbits squirrels woodchucks muskrats skunks coyotes foxes opossums mice rats quail chickens pheasants snakes ticks and flies The Rocky Mountain tick Western wood tick Eastern dog tick and the Lone Star tick (*Dermacentor andersoni D variabilis D occidentalis* and *Amblyomma americanum*) may act as reservoirs of infection One species of deer fly (*Chrysops discalis*) and a mosquito (*Aedes cinereus* in Sweden) can transmit tularemia to man Ticks are an important reservoir of the disease because the microorganism is transferred transovarially from the female to her progeny Sporadic and epidemic tularemia have occurred following contact with water and fish contaminated by infected animal carcasses However human to human transmission of infection probably does not occur Wild cottontail rabbits are the principal source of tularemia in the United States

Man is highly susceptible to tularemia the organism usually invades through the skin mucous membrane or gastrointestinal tract Hunters butchers and housewives are most often affected through exposure to infected animals

Pathology Microscopically the primary cutaneous lesion shows neutrophilic infiltration granulomatous reaction and necrosis The regional lymph nodes develop similar changes and often suppurate The granulomatous reaction in tularemia consists of giant and epithelioid cells and lesions resembling tubercles may occur in liver spleen lung and kidney *Pasteurella tularensis* has been recovered from lymph nodes many days after apparent subsidence of the disease

Manifestations The incubation *period is 3 to 7* days A typical lesion of skin or mucous membranes is not invariably present and therefore tularemia has classically been separated into several clinical types

More than 80 per cent of *infections by Past tularensis* are associated with a *lesion of* the skin or mucous *membranes* which has no distinguishing characteristics It begins as a reddened papule that may be pruritic and soon ulcerates The *primary* lesion in this *ulceroglandular* form of the disease is rarely very painful is usually *present before* onset of systemic symptoms *and may not heal* until

mycin is a poor therapeutic agent in brucellosis because while the antibiotic is quite lethal for extracellular brucellae intracellular brucellae are protected against the drug But there is no question that simultaneous treatment with streptomycin or dihydrostreptomycin and sulfadiazine is much more effective in human brucellosis than the administration of either the antibiotic or sulfonamide alone Streptomycin or dihydrostreptomycin can be given intramuscularly in a dose of 0 5 Gm every 12 hr for 2 weeks At the same time 1 Gm sulfadiazine is administered orally four times daily and continued for 3 weeks

Although the combination of streptomycin and sulfadiazine proved to be a definite advance in the therapy of brucellosis superior results have been obtained with the use of chlortetracycline (Aureomycin) *administered orally in a dose of 0 5 Gm* four times daily for a minimum of 3 weeks Relapses can often be treated successfully with a second course of chlortetracycline Similar results can be obtained with oxytetracycline (Terramycin) using the same doses Chloramphenicol (Chloromycetin) does not appear to be so satisfactory an antibiotic for brucellosis as the tetracyclines and its use is not recommended

There is evidence that *a combination of streptomycin or dihydrostreptomycin with one of the tetracycline drugs* provides a more efficient form of therapy than the tetracyclines alone The policy at the University of Minnesota clinics is to use one of the tetracycline antibiotics alone for the average case of brucellosis due to *Br abortus* in doses as recommended above However for more severe cases and for all those due to *Br melitensis* or *Br suis* streptomycin or dihydrostreptomycin is given intramuscularly in a dose of 0 5 Gm every 12 hr for 2 weeks along with an oral dose of 0 5 Gm tetracycline administered four times daily Treatment with the latter drug is usually kept up for 3 weeks

Patients with acute brucellosis often exhibit a severe toxic state which simulates typhoid fever and which gradually subsides after several days of therapy with antibiotics *However rapid and dramatic improvement* occurring within 8 to 12 hr can be obtained with the use of one of the adrenocorticoid steroid preparations An initial dose of *100 mg hydrocortisone can be given intravenously* followed by an oral dose of 25 mg four times daily Cortisone can also be employed orally in a dose of 50 mg four times daily Any steroid therapy should be discontinued after 72 to 96 hr and appropriate antibiotics should always be administered simultaneously

A common therapeutic practice in the more chronic cases is to attempt desensitization of the tissues to *Brucella* by treating patients with one of the several antigenic preparations such as heat killed *Brucella* cells or filtrates of *Brucella* cultures While hypersensitivity to *Brucella* is a factor in the symptomatology and the use of ascending doses of antigenic material may be sound therapy the results are difficult to evaluate and treatment must often be continued for several months Violent local and systemic reactions often occur even following the *injection of minute amounts of antigen*

For the relief of headache and the generalized aches and pains salicylates may be prescribed the occasional use of barbiturates is desirable for the insomnia which is so commonly a part of the disease

Prognosis While brucellosis may be a chronic and disabling disease the over all mortality rate is not more than 2 to 3 per cent and is negligible *when appropriate antibiotic therapy is promptly* employed The physician today may learn a great deal about the prognosis of this disease by turning back and looking over the rich experience of the Mediterranean Fever Commission which was recorded in 1905 to 1907 In a day when specific treatment was lacking careful clinical observations were made In an analysis of hundreds of *Br melitensis* cases Eyre stated the following in 1908

> *One may safely say that not more than 10 per cent* are convalescent in a shorter period than one month from the onset of symptoms In 50 per cent the disease extends over two months in 25 per cent to three months and in fully 15 per cent a duration of three months is exceeded

Over the succeeding years it has been observed *that a relatively small but important number* of cases will have a protracted illness Cases of bacteriologically proved brucellosis in which the disease has continued for over a year have been studied at the University of Minnesota Hospitals But such cases are not commonly encountered One cannot escape the conviction that so called chronic brucellosis is being mislabeled too often on the basis of procedures of doubtful value especially *the intradermal test with Brucella* antigen

Relapses do occur in the more chronic cases of brucellosis These recurrences are manifested by fever and by mental and physical disability with generalized aches and pains But too little attention has been given to the problem of reinfections Clinical observations in meat packing plant employees have confirmed studies made with experimentally infected animals in that the immunity induced by one attack of brucellosis is only relative Second and third infections do take place Thus in individuals who continue to be exposed to the disease it may be quite difficult to differentiate between relapses and reinfections

tious the hazards of isolating it have been over emphasized and with reasonable care accidental infection of personnel in diagnostic laboratories is unlikely

Skin test with a diluted suspension of killed *Past tularensis* or purified antigen becomes positive during the first week of disease The cutaneous response is delayed and resembles the tuberculin reaction

The total blood leukocyte count is usually normal The erythrocyte sedimentation rate is normal in ulceroglandular or mild disease but is frequently elevated in severe typhoidal tularemia

Differential Diagnosis Brucellosis typhoid fever disseminated tuberculosis the early stage of several rickettsial diseases and infectious mononucleosis can closely resemble typhoidal tularemia History of possible contacts is important and appropriate serologic and cultural studies are usually successful in differentiating these infections Pneumonic tularemia must be distinguished from viral mycotic and other bacterial infections of the lung The differential diagnosis of pneumonia is discussed in Chap 111 (p 835) Oculoglandular syndromes likely to be confused with tularemia are described in Chap 192 (p 1102)

The common ulceroglandular type of tularemia must be distinguished from a variety of infections in which a local cutaneous ulcer with regional lymphadenopathy can occur Besides ordinary pyoderma caused by streptococci or staphylococci these include lymphogranuloma venereum (p 1096) cat scratch fever (p 1098) rat bite fever (p 1019) bubonic plague (p 907) anthrax (p 913) glanders (p 911) several rickettsioses of which the important one in this country is rickettsialpox (p 1031) several viral infections of the skin such as orf cowpox etc (pp 1104 1062) and inoculation syphilis or tuberculosis In all these with the exception of lymphogranuloma venereum and cat scratch fever the regional lymph node involvement is usually proportional to the size of the cutaneous ulcer Extragenital lymphogranuloma is rare fever and systemic symptoms in cat scratch fever are rarely severe for more than a few days

Treatment Streptomycin is the antibiotic of choice for tularemia The dosage is 0 5 to 1 0 Gm every 12 hr for 7 to 10 days Response to treatment is almost invariably prompt *Pasteurella tularensis* cannot be recovered from lymph nodes or skin lesions after 24 to 48 hr of therapy However the regional lymph nodes may continue to enlarge and suppurate for several days Pulmonary lesions usually subside rapidly although the evolution of the cutaneous lesion is not interrupted The tetracycline antibiotics chloramphenicol and novobiocin are also effective although disappearance of fever and symptoms may not occur so rapidly as with streptomycin Aspiration of pus from suppurating nodes is rarely necessary if fistulas persist total surgical removal of the involved tissue can be carried out Surgery may be followed by transient recurrence of fever despite failure to demonstrate the organism in excised tissues

Prophylaxis A vaccine developed by Foshay may possibly provide protection against the occurrence of infection and definitely reduces the severity of the disease The vaccine stimulates serum agglutinins and induces positive skin reactions to the bacterial antigens Its use is recommended for hunters butchers and laboratory workers exposed to the organism Avoidance of contact with possible sources of infection is important in prophylaxis and the incidence of the disease in several localities has fallen sharply with the introduction of laws prohibiting the sale of wild rabbits by butchers

Prognosis The mortality rate in untreated tularemia is 6 to 7 per cent However with specific antimicrobial therapy death is rare A fatal outcome is more likely in typhoidal tularemia than in other types possibly because the disease may be unrecognized

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129 PLAGUE
Edward S Miller

Definition Human plague is an acute severe frequently fatal infection characterized by fever prostration, and suppurative lesions of the lymphatic system Sometimes there is an associated pneumonia *Pasteurella pestis* is the etiologic agent rodents are the primary hosts and the usual vectors are fleas

History Plague is one of the ancient pestilences of man Descriptions of a plaguelike disease are found in the Old Testament Early Greek and Roman manuscripts testify to its existence in the

convalescence is well under way Frequently it is overlooked or its relationship to severe systemic symptoms is not recognized Regional lymph node enlargement is a constant feature and is usually more prominent than that accompanying infections of similar severity produced by other microorganisms The involved nodes are often exquisitely tender and fluctuant The overlying skin may be hot and reddened Fistula formation and drainage can occur spontaneously Generalized lymphadenopathy *is present in some cases* but the *regional* nodes are most prominently involved There is considerable variation in the intensity of the systemic symptoms of ulceroglandular tularemia the patient may be almost asymptomatic or severely prostrated Clinical and roentgenographic evidence of pneumonitis can accompany this form of the disease illustrating its disseminated character but bacteremia is rarely demonstrable

Localized lymph node enlargement but without detectable skin lesion is referred to as *glandular* tularemia The pathogenesis of this form of the disease is probably identical to that of ulceroglandular tularemia and the features of the illness are also the same

Rarely the portal of entry of the organism is the conjunctiva where there develops an ulcer with edema congestion lacrimation photophobia and pain In this *oculoglandular* type of tularemia the preauricular submaxillary and anterior cervical lymph nodes enlarge in some patients Corneal ulceration and scarring or perforation of the globe can occur

Ingestion of contaminated meat or water can result in primary lesions of tularemia in the *gastrointestinal* tract This rare form of the disease is characterized by pronounced diarrhea abdominal pain nausea vomiting melena and hematemesis but otherwise differs little from tularemia introduced through other portals Ulcerative lesions are often found in the buccal mucosa pharynx or intestine and the mesenteric or cervical lymph nodes are involved early in the disease

Tularemia without obvious primary ulcer or localized lymphadenitis is referred to as the *typhoidal* type Constitutional symptoms in typhoidal tularemia differ in no way from those in other types of the disease although patients are as a rule more prostrated In the absence of localized manifestations the clinical recognition of tularemia is of course more difficult and diagnosis is likely to depend principally upon serologic tests or isolation of the organism

Pneumonia can accompany any of the various clinical types of tularemia Involvement of the lung is secondary to hematogenous dissemination in situations where infection is probably acquired by inhalation of the organism (as in bacteriology laboratories) there is no convincing evidence that primary tularemic pneumonia occurs Pneumonitis in tularemia can lead to prominent signs of cough mucoid sputum hemoptysis pleuritic pain dyspnea and cyanosis but extensive x ray evidence of pneumonitis is sometimes present in the absence of any symptoms of pulmonary disease Physical findings often correlate poorly with the roentgenologic changes which consist of diffuse patchy or lobar infiltrations and inconstant hilar adenopathy Pleural effusion can occur in tularemic pneumonia but lung abscess is rare

Among the unusual infections produced by *Past tularensis* are endocarditis pericarditis peritonitis appendicitis osteomyelitis and meningitis

Fever in tularemia develops abruptly often with rigors and in the untreated patient may persist at levels of 104 to 106 F for as long as 4 weeks The fever is sustained or mildly remittent and defervescence is by lysis Headache myalgia anorexia, and nausea are common

Splenomegaly of moderate degree is detectable in many patients An evanescent macular or papular *rash* is sometimes present on the trunk and extremities early in the disease

Convalescence in untreated tularemia is prolonged and fever lassitude fatigability myalgia irritability or anorexia may persist or recur for many months Recovery is usually prompt if acute tularemia is treated with antibiotics before the third week of disease When therapy is delayed beyond this period patients are more likely to be left with mild debilitation that is unresponsive to further administration of antimicrobial drugs

Recovery from tularemia is usually followed by immunity in the sense that recurrence of severe disease is unlikely However immunity to reinfection is not complete and several instances of second even third attacks of tularemia have been recorded Almost invariably they have consisted of the development of a local lesion and mild regional adenopathy without systemic symptoms and with little or no fever

Laboratory Findings Agglutinins for *Past tularensis* are present in serum after the second week of illness Although it has been said that cross agglutination may occur with antigens of *Brucella* this is by no means a constant finding

Pasteurella tularensis can be recovered from the infected patient by appropriate cultures or animal inoculation It is rarely found in blood cultures but it can be isolated from the mucocutaneous ulcer or regional lymph nodes with regularity The organism has been cultured from the sputum and gastric washings in several patients some of whom have shown no roentgenographic evidence of pneumonitis this can be a useful diagnostic procedure Although *Past tularensis* is highly infec

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Definition Human plague is an acute severe frequently fatal infection characterized by fever prostration and suppurative lesions of the lymphatic system Sometimes there is an associated pneumonia *Pasteurella pestis* is the etiologic agent, rodents are the primary hosts and the usual vectors are fleas

History Plague is one of the ancient pestilences of man Descriptions of a plaguelike disease are found in the Old Testament Early Greek and Roman manuscripts testify to its existence in the

convalescence is well under way Frequently it is overlooked or its relationship to severe systemic symptoms is not recognized Regional lymph node enlargement is a constant feature and is usually more prominent than that accompanying infections of similar severity produced by other microorganisms The involved nodes are often exquisitely tender and fluctuant *The overlying skin may be* hot and reddened Fistula formation and drainage can occur spontaneously Generalized lymphadenopathy *is* present in some cases but the regional nodes are most prominently involved There is considerable variation in the intensity of the systemic symptoms of ulceroglandular tularemia the patient may be almost asymptomatic or severely prostrated Clinical and roentgenographic evidence of pneumonitis can accompany this form of the disease illustrating its disseminated character but bacteremia is rarely demonstrable

Localized lymph node enlargement but without detectable skin lesion is referred to as *glandular* tularemia The pathogenesis of this form of the disease is probably identical to that of ulceroglandular tularemia and the features of the illness are also the same

Rarely the portal of entry of the organism is the conjunctiva where there develops an ulcer with *edema congestion lacrimation photophobia and* pain In this *oculoglandular* type of tularemia the preauricular submaxillary and anterior cervical lymph nodes enlarge in some patients Corneal ulceration and scarring or perforation of the globe can occur

Ingestion of contaminated meat or water can result in primary lesions of tularemia in the *gastrointestinal* tract This rare form of the disease is characterized by pronounced diarrhea abdominal pain nausea vomiting melena and hematemesis but otherwise differs little from tularemia introduced through other portals Ulcerative lesions are often found in the buccal mucosa pharynx or intestine and the mesenteric or cervical lymph nodes are involved early in the disease

Tularemia without obvious primary ulcer or localized lymphadenitis is referred to as the *typhoidal* type Constitutional symptoms in typhoidal tularemia differ in no way from those in other types of the disease although patients are as a rule more prostrated In the absence of localized manifestations the clinical recognition of tularemia is of course more difficult and diagnosis is likely to depend principally upon serologic tests or isolation of the organism

Pneumonia can accompany any of the various clinical types of tularemia Involvement of the lung is secondary to hematogenous dissemination Even in situations where infection is probably acquired by inhalation of the organism (as in bacteriology laboratories) there is no convincing evidence that primary tularemic pneumonia occurs Pneumonitis in tularemia can lead to prominent signs of cough *mucoid sputum hemoptysis* pleuritic pain dyspnea and cyanosis but extensive x ray evidence of pneumonitis is sometimes present in the absence of any symptoms of pulmonary disease *Physical findings* often correlate poorly with the roentgenologic changes which consist of diffuse patchy or lobar infiltrations and inconstant hilar adenopathy *Pleural* effusion can occur in tularemic pneumonia but lung abscess is rare

Among the unusual infections produced by *Past tularensis* are endocarditis pericarditis peritonitis appendicitis osteomyelitis and meningitis

Fever in tularemia develops abruptly often with rigors and in the untreated patient may persist at levels of 104 to 106 F for as long as 4 weeks The fever is sustained or mildly remittent and defervescence is by lysis Headache myalgia anorexia and nausea are common

Splenomegaly of moderate degree is detectable in many patients An evanescent macular or papular *rash* is sometimes present on the trunk and extremities early in the disease

Convalescence in untreated tularemia is prolonged and fever lassitude fatigability myalgia *irritability or anorexia may persist or recur for* many months Recovery is usually prompt if acute tularemia is treated with antibiotics before the third week of disease When therapy *is delayed beyond* this period patients are more likely to be left with mild debilitation that is unresponsive to further administration of antimicrobial drugs

Recovery from tularemia is usually followed by immunity in the sense that recurrence of severe disease is unlikely However immunity to reinfection is not complete and several instances of second and even third attacks of tularemia have been recorded Almost invariably they have consisted of the development of a local lesion and mild regional adenopathy without systemic symptoms and with little or no fever

Laboratory Findings Agglutinins for *Past tularensis* are present in serum after the second week of illness Although it has been said that cross agglutination may occur with antigens of *Brucella* this is by no means a constant finding

Pasteurella tularensis can be recovered from the infected patient by appropriate cultures or animal inoculation It is rarely found in blood cultures but it can be isolated from the mucocutaneous ulcer or regional lymph nodes with regularity The organism has been cultured from the sputum and gastric washings in several patients some of whom have shown no roentgenographic evidence of pneumonitis this can be a useful diagnostic procedure Although *Past tularensis* is highly infec

leys radiating from these regions Sylvatic plague is dependent on other arthropod vectors and other rodent hosts and therefore has a somewhat different and wider distribution Since susceptible hosts exist in all parts of the country the appearance of this disease elsewhere is a likely possibility Vigorous rat and flea control measures have eliminated rat plague whenever it has made its appearance in American cities However sylvatic plague is impossible to eradicate and offers a constant threat of extension back to the urban rat population

Pathogenesis Following the bite of an infected flea organisms are carried by the lymphatics to the thoracic duct and thence to the blood stream There is a brief initial bacteremia during which organisms are disseminated to all the organs The chief defense of the body is the mechanism of phagocytosis aided by the development of circulating antibodies which react with the capsular substance of the organisms and thus facilitate phagocytosis Plague infection is accompanied by the production of an endotoxin which has seriously damaging effects on the tissues of the host Modern chemotherapeutic agents may result in control of the infection bacteriologically yet the patient may die from the toxemia

The most prominent lesions are ordinarily in the lymphatic system In bubonic plague a hemorrhagic zone of edema surrounds an inflamed and suppurating group of regional lymph glands The latter are hyperplastic and show areas of focal necrosis containing many organisms Similar metastatic lesions may develop in distant groups of glands or in other viscera In pulmonic infections there is a lobular pneumonia with hemorrhagic exudate in the alveolar spaces with accompanying pleuritis and bronchitis Hemorrhages may be found in any organ or beneath epithelial surfaces

Manifestations Symptoms appear after an incubation period of from 1 to 12 days The disease can assume several different clinical forms of which the *bubonic* variety is the most common Illness begins abruptly with chills a rise in temperature to 102 to 105 F tachycardia headache vomiting uncertain gait marked prostration and delirium The spleen is sometimes palpable The flea bite which represents the portal of entry rarely can be seen if present it is marked by a papule or vesicle which ultimately becomes pustular Pain and tenderness point to the regional glandular lesions which give the disease its name They are in the inguinal or femoral regions in the majority of cases less often in the axilla or neck and are uncommon elsewhere The infection may extend secondarily to other superficial or deeply situated groups of glands The bubo consists of a firm matted group of glands measuring from 2 to 5 cm in diameter and surrounded by a boggy and frequently hemorrhagic zone of edema It usually suppurates and drains spontaneously after 1 or 2 weeks though in some instances there is complete resorption

There is a marked hemorrhagic tendency presumably due to an endotoxic effect on blood vessels Petechiae or ecchymoses are often seen beneath cutaneous or mucous surfaces Bleeding may occur into a viscus or a serous cavity or from the nose alimentary respiratory or urinary tracts

The course of bubonic plague is marked by an irregular or remittent fever It often drops at the time of appearance of the bubo only to rise again In favorable cases the temperature falls gradually during the second week concomitant with improvement in the general clinical condition A rise to hyperpyrexic levels or a precipitous fall to normal or to subnormal frequently heralds approaching death Most fatalities occur during the first week of illness Though bubonic plague is usually a severe illness mild cases are sometimes seen during epidemics to these is applied the name *pestis minor*

The second clinical form of plague is the so called primary *septicemic* form which is actually a variant of bubonic plague The patient experiences a sudden and overwhelming systemic illness There is a marked constitutional reaction with chills fever rapid pulse severe headache nausea vomiting and delirium Death terminates the course within a few days before localizing lesions become clinically apparent Nevertheless autopsy usually reveals inflammation in some part of the lymphatic system

The third form which plague may take is that of *pneumonia* The initial cases appear in patients with bubonic plague of whom as many as 5 per cent develop secondary lesions in the lungs These individuals may provide the starting point for a man to man epidemiologic cycle of air borne primary pneumonic plague It is a fulminating infection accompanied by great prostration cough dyspnea and in the later stages cyanosis The sputum is abundant bloodstained and teeming with *Past pestis* Often there are no clear cut pulmonary signs though scattered rales or areas of dullness may be found In the absence of specific therapy plague pneumonia invariably ends in death within 1 to 5 days

The infectious process may localize in other regions of the body Subcutaneous abscesses and cutaneous ulcerations sometimes occur and the meninges are occasionally invaded

Laboratory Findings Since plague is an uncommon disease in the United States the diagnosis often has been overlooked until the patient has succumbed or until multiple cases have developed Nevertheless the epidemiology and the clinical

Mediterranean region long before the Christian era For many centuries the disease was endemic in Asia and in Europe where from time to time great pandemics destroyed large segments of the human population The last major outbreak originated in China in the late nineteenth century spread to all the continents and was first recognized in the United States in 1900 Some authorities believe that it was initially introduced into this country at that time through the Port of San Francisco However other evidence suggests that rodent plague actually was present long before In any event it has certainly now become well established

Etiologic Agent *Pasteurella pestis* is an encapsulated nonmotile gram negative bacterium which produces no spores and will grow under either aerobic or anaerobic conditions Though it is predominantly bacillary in shape coccal ovoid and other pleomorphic forms are often seen When stained with carbolfuchsin or carbolthionin the organisms display a characteristic bipolar appearance Growth occurs on ordinary media On agar the colonies are small round transparent colorless and viscous There are no important antigenic differences among strains collected from different animal species in various parts of the world

Epidemiology As with other infectious organisms spread through the agency of vectors *Past pestis* is enabled to survive and be transmitted by means of a series of intricate ecologic adaptations Plague is fundamentally an affection of rodents from them it is sometimes and quite incidentally transmitted to man Rats are the most important animal hosts because they are found all over the world travel widely and live in close association with man In rural or wooded regions plague may be enzootic in many other species of rodent hosts Such infection is referred to as *sylvatic plague* in contrast to *rat* or *murine plague* In the United States alone the endemic reservoir includes at least 38 species of rats mice marmots owls gophers badgers rabbits prairie dogs squirrels and chipmunks Urban plague follows a different epidemiologic pattern from rural plague Large outbreaks in man usually arise in urban areas and in the wake of rat epizootics Under circumstances of poor sanitation a concentration of people and of rats provides opportunity for the transmigration of parasites from rats to man An epizootic of sylvatic plague may encompass a number of different rodent species in an area and may involve a complex exchange of ectoparasites Such outbreaks may be devastating to the rodent populations yet they give *rise only to sporadic human cases simply because* man rarely comes into close contact with these animals Since 1900 approximately 500 cases of human plague have been reported in the United States more than *400* of these developed in association with murine plague while less than 100 resulted from contact with sylvatic plague

The flea is the usual transmitting agent In murine and human infections the most important species is the Oriental rat flea *Xenopsylla cheopis* Other arthropods occasionally function as vectors including lice ticks and possibly bedbugs The flea becomes infected by ingesting the blood of a bacteremic animal The organisms multiply in the alimentary tract of the insect and eventually plug the stomach so that no more blood can enter When the flea feeds on a new host the bite wound is inoculated by the regurgitation of organisms or as a result of mechanical contamination by the mouth parts Plague bacilli are also present in flea feces and infection may follow the scratching of this material into the skin Oriental rat fleas will accept other hosts including man particularly if rats are not immediately available When an epizootic decimates the rat population fleas are encouraged to transfer from the dead rodents to humans

Human bubonic plague results chiefly from the bite of the rat flea Infection can also be acquired by direct contact with the tissues of an infected animal or by its bite for the organisms can penetrate through skin abrasions and through intact mucous membranes Not a few accidental infections have occurred in laboratory workers as a result of handling cultures and infected animals Direct transmission of the bubonic form of the disease from man to man is unusual in contradistinction to the mode of spread of primary pneumonic plague The latter type of epidemic is initiated by a patient with bubonic disease who develops a secondary plague pneumonia and therefore excretes large quantities of organisms in his sputum The infection may then be air borne in droplet nuclei directly to a human contact This type of plague is highly contagious secondary cases are common among those attending a patient and under suitable circumstances tremendous outbreaks may occur

Plague is widely and permanently entrenched in the rodent population of the United States chiefly in the West Infected animals have been found in California Oregon Washington Utah Idaho Nevada New Mexico Arizona Texas Michigan Louisiana Florida Colorado Montana Oklahoma Kansas North Dakota and Wyoming Human cases have occurred in the first 12 of these states Recent studies emphasize the close relationship between the distribution of murine plague and that of the Oriental rat flea This flea flourishes in areas where optimal climatic conditions of mean temperature and humidity prevail In the United States these areas include the Pacific Coast region the Gulf and southern Atlantic Coast states and certain val

130 GLANDERS
Edward S Miller

Definition and Etiology Glanders is a grave infectious disorder characterized by the development of numerous granulomatous abscesses throughout the body The causative agent is *Malleomyces mallei* a small aerobic nonmotile nonsporulating gram negative bacillus

Epidemiology and Pathogenesis This is another of the group of infectious diseases of animals which are sometimes transmitted to man In this instance the principal natural hosts are horses mules and asses Glanders once was a common equine disease in America but stringent control measures have virtually eradicated it However it is still prevalent in certain sections of Central Europe North Africa and Asia The infection may be acquired by handling diseased animals Organisms gain entry through cutaneous abrasions by implantation on the conjunctiva by ingestion or by inhalation Human beings are highly susceptible as evidenced by the large number of laboratory workers who have contracted the disease With the elimination of animal glanders in the United States the infection has become rare in man also

Manifestations Human glanders usually runs an acute and stormy course After an incubation period of several days to several weeks illness begins abruptly with chills high fever and marked prostration At the portal of entry commonly on the skin a nodule forms and breaks down to become a painful ulcer Such ulcers show irregular sharply demarcated borders with little tendency to heal The regional lymph nodes are involved and lymphatic and vascular dissemination soon results in a generalized spread Miliary lesions develop along the course of lymphatics in subcutaneous and submucous tissues in muscle in the lungs and in other viscera The lesions gradually enlarge coalesce and undergo central caseous necrosis The superficial nodules ulcerate while more deeply situated abscesses often form fistulous tracts which exude discharges onto the surface Areas of consolidation appear in the lungs and the liver and the spleen become inflamed and enlarged Many patients exhibit ulcerations of the upper respiratory tract with erosion of adjacent cartilaginous and bony structures An eruption sometimes becomes evident either localized to one area or generally distributed At first it is a macular rash then it becomes papular and pustular and the lesions may ulcerate Among other septic manifestations are meningitis osteomyelitis and purulent polyarthritis Infection may extend to the sinuses ears conjunctiva mouth pharynx, and trachea

Acute glanders progresses with great rapidity ending fatally in 1 to 3 weeks in the majority of cases A milder syndrome has been described in a group of laboratory workers who were accidentally infected via the respiratory tract In these cases the clinical picture was not unlike that of viral pneumonia of average severity and all patients recovered

A chronic form of glanders sometimes is seen The onset is generally insidious with low grade fever and mild initial symptoms The course is characterized by exacerbations and remissions and punctuated by the irregular appearance of painful ulcers and draining abscesses Chronic glanders may at any time assume the fulminating qualities of the acute form More than half the patients die after months or years of exhausting illness

Diagnosis Specific diagnosis can be established by culture by animal inoculation by serologic testing by the demonstration of dermal sensitivity and by biopsy *Malleomyces mallei* can be recovered from exudates sputum scrapings from a local lesion and terminally from the blood Strauss reaction is elicited by injecting infected material into the peritoneal cavity of a male hamster or a male guinea pig Scrotal swelling becomes apparent in 2 to 4 days and organisms then can be recovered from the tunica vaginalis Both agglutinating and complement fixing antibodies appear in the blood during the second to fourth weeks of illness they are specific when present in high titer (agglutination titer of 1 640 or higher complement fixing titer of 1 20 or higher) except for some cross reaction with the antigens of *Malleomyces pseudomallei* The latter organism causes melioidosis a disease closely related to glanders (see p 912) Patients who survive the initial onslaught of illness develop a persistent skin sensitivity to mallein which is an antigen prepared from cultures of *M mallei* The test is performed by intradermal injection of 0 1 ml of a 1 10 000 dilution of commercial mallein it is considered positive if an erythema is present 48 hr later Skin and mucous membrane lesions show characteristic histologic features and are readily accessible to biopsy

Treatment Sulfadiazine has proved to be a potent chemotherapeutic agent in experimental animal infections and has been used successfully in several human cases The drug should be administered for a minimum of 20 days in doses sufficient to maintain blood levels of 10 to 15 mg per 100 ml Penicillin is ineffectual Streptomycin was of only slight benefit in an experimental study but appeared to be useful in the treatment of one reported human case Little or no information is available on the therapeutic activity of the newer antibiotics It is evident that strains isolated from

features provide highly characteristic leads to the clinician Once a suspicion of plague is entertained it can readily be verified by smear culture and animal inoculation of appropriate specimens If a bubo is present a small quantity of interstitial fluid should be aspirated from its center Large numbers of morphologically characteristic bacilli are usually seen in a stained smear Infected sputum likewise contains many organisms Bacteremia of varying degrees occurs at some time during the course of nearly all cases Pus and sputum should be cultured on blood agar plates while blood is inoculated into hormone cystine or other nutrient broth Organisms are identified by their morphologic and colonial characteristics and by agglutination with specific antiserum Guinea pig inoculation is the final step in identification In this animal the gross and micro scopic lesions are highly characteristic It is to be emphasized that the handling of infected materials or animals involves great danger of infection of the laboratory workers Except as mentioned above serologic tests have not been satisfactory or useful in diagnosis

The white blood cell count is elevated to levels of 20 000 to 40 000 with a predominance of poly morphonuclear leukocytes There is little or no change in the red blood corpuscles

Differential Diagnosis Before the appearance of localizing signs plague may be confused with severe systemic illnesses such as typhoid or typhus The bubonic form bears certain resemblances to other varieties of infectious lymphadenitis includ ing tularemia syphilis and lymphogranuloma venereum and to those of staphylococcal or strep tococcal origin Pneumonic plague must be distin guished from tularemic pneumococcal and other bacterial pneumonias as well as from psittacosis and primary atypical pneumonia A consideration of epidemiologic factors plus bacteriologic studies will aid in the differentiation

Treatment The therapy and the prognosis of plague have been vastly improved by the intro duction of streptomycin and other chemothera peutic agents Even pneumonic and septicemic cases can be salvaged *if treatment is initiated early* (within the first 20 hr after onset) Streptomycin is the drug of choice it is given in divided doses of 2 to 4 Gm daily until the patient has been *afebrile at least 3 days* Sulfadiazine is almost as effective in uncomplicated bubonic plague but definitely less so in septicemic and pneumonic cases Chloramphenicol oxytetracycline chlortetracycline neomycin and polymyxin are all potent antiplague substances the first two have been used success fully in treating pneumonic plague Antiplague serum also has value as an antitoxic agent Various combinations of these medicines can be used to advantage depending on their availability the severity of illness and the duration of illness before treatment is begun

Buboes are treated with hot moist applications Incision and drainage should be postponed until the lesion becomes well localized

Prophylaxis and Control The control of plague in endemic urban areas demands unceasing vigi lance in detecting rodent epizootics and vigorous measures in combating outbreaks The most im portant control measures are those aimed at ex termination of rats and their ectoparasites Rats are attacked by poisoning and trapping by elimination of harborage areas and by separating them from their food supplies DDT has been used with bril liant success in diminishing the flea population in festing both rodents and human beings thereby interrupting the rat flea rat and the rat flea man cycles of transmission

The elimination of sylvatic plague is an impos sible task For protection of the individual reliance must be placed on avoidance of contact with wild rodents For protection of a community within an endemic area it is essential to eradicate rodents within the city and to maintain a rodent free belt surrounding it

Patients must be disinfested and carefully iso lated while other intimately exposed persons should be quarantined Excellent prophylaxis is provided by administering sulfadiazine to contacts in a dose of 3 Gm a day this often protects even against ex posure to pneumonic patients Two types of bac terial vaccines are in use one composed of dead organisms and the other containing a special aviru lent strain of living bacilli Both provide limited and transitory active immunity General vaccina tion of a population is a *worthwhile procedure in* an area under threat of an epidemic

Prognosis Formerly the fatality rate of bubonic plague averaged 50 to 90 per cent while the *pneumonic septicemic and meningitic forms* were almost invariably fatal However even the gravest varieties of infection respond to chemotherapy The over all fatality rate has been reduced to 5 to *10 per cent.*

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Section 6 Miscellaneous Bacterial Infections

132 ANTHRAX

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Definition Anthrax (malignant pustule charbon, splenic fever milzbrand woolsorters disease) is a disease of wild and domesticated animals that is transmitted to man by contact with infected animals or their products and rarely by insect vectors which act as mechanical carriers of the etiologic organism The characteristic lesion of human anthrax is a necrotic cutaneous ulcer the malignant pustule"

Etiology *Bacillus anthracis* is a large encapsulated gram positive aerobic spore forming microorganism that grows well in most nutrient media Its pathogenicity for laboratory animals differentiates it from *Bacillus subtilis* which it closely resembles The spores are killed by boiling for 10 min but can survive for many years in soil and in animal products an important factor in persistence and spread of the disease The bacillus was identified by Royer and Davaine in sheep in 1849 and was therefore the first causative agent of an infectious disease ever demonstrated The classic studies of Robert Koch in 1877 showing that *B anthracis* was indeed the cause of anthrax serve as the prototype for the establishment of etiology of infectious diseases

Epidemiology Anthrax is world wide repeated outbreaks have occurred in Southern Europe Africa Australia Asia and on both American continents

Cattle horses sheep goats and swine are most commonly infected Between 1945 and 1955 there were 3 447 recognized outbreaks of anthrax among animals in the United States centering mostly in South Dakota Nebraska Arkansas Mississippi Louisiana Texas and California The tendency of the disease to occur in animals in late summer and early fall is related to grazing conditions and the abundance of flies

The disease in man is acquired by butchering skinning or dissecting infected carcasses or by handling contaminated hide wool hair or other materials It is seen principally in agricultural and industrial employees Of the 183 reported cases of human anthrax in this country between 1945 and 1955 the majority involved workers handling imported and unprocessed wool hair or hides The usual form of human disease follows inoculation of bacilli or spores into the skin often, if not always through a wound or abrasion However intestinal infection has followed ingestion of contaminated meat and anthrax has been thought to develop after inhalation of spores

Pathogenesis The "malignant pustule" which follows cutaneous inoculation of anthrax organisms is characterized microscopically by vesiculation neutrophilic infiltration and gelatinous edema in surrounding structures Suppuration is rare in the absence of secondary pyogenic infection Spread of the bacilli to the regional lymph nodes may be followed by systemic dissemination Examination of tissues from fatal human cases reveals masses of the bacteria in blood vessels lymph nodes parenchyma of various organs and in connective tissues There is scanty or absent cellular exudation at these foci the predominant changes being widespread hemorrhage and edema So-called anthrax pneumonia" and "anthrax meningitis are in all probability an expression of this generalized hemorrhage and edema in an easily detectable clinical site rather than selective localization of bacterial multiplication in these tissues

Although it was at one time thought that in anthrax death might be the result of occlusion of vessels by masses of bacilli studies have now shown that the blood of fatally infected experimental animals contains a lethal toxin which can be neutralized by appropriately prepared antiserums This toxin has not been isolated with regularity in vitro and its exact role in the pathogenesis of the disease requires further study

Manifestations The malignant pustule" of human anthrax begins usually on an exposed body surface as a painless pruritic erythematous papule which soon vesiculates and ulcerates to form a black eschar Tiny satellite vesicles are frequent The ulcer may be surrounded by extensive edematous swelling which is nontender nonpitting and so characteristic of anthrax that it is a valuable diagnostic sign After about 5 days the ulcer begins to subside but edema may persist for many days or even weeks Mild tenderness and enlargement of regional lymph nodes is frequently present but the involvement is not so striking as in tularemia or cat scratch disease Constitutional symptoms are often absent despite extensive local changes but there may be mild fever headache and malaise In the infrequent fulminant case of disseminated anthrax high fever prostration and a rapidly fatal course are seen So called woolsorters disease" a highly fatal disseminated infection is

patients should be subjected to careful studies of in vitro sensitivities and treatment should be guided thereby Other antibiotics singly or in combination may prove even more effective than sulfadiazine

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131 MELIOIDOSIS

Edward S Miller

Definition Melioidosis is a fulminating usually fatal infectious disease in which granulomatous lesions develop throughout the body Etiologically pathologically and clinically it bears a striking resemblance to glanders

Etiology The causative organism is *Malleomyces pseudomallei* a motile aerobic gram negative bacillus This bacterium is closely related to *Malleomyces mallei* the causative agent of glanders but the two can be differentiated by bacteriologic and serologic methods There is also an important epidemiologic difference for the primary hosts and principal reservoir of melioidosis are rats whereas glanders is chiefly an affection of horses The mode of transmission has not been established but is believed to occur via contamination of food and water with the excreta of infected rodents the portal of entry being the alimentary tract

Epidemiology The disease was first identified in Rangoon in 1911 and some 300 cases have since been observed in Indo China the Malay States Thailand Ceylon and contiguous regions It may have a broader geographic distribution than has heretofore been suspected for cases have been reported as originating in Guam and in the United States

Manifestations The clinical course of melioidosis is much like glanders except that it is even more virulent and lethal Nearly all untreated cases have ended fatally *In the most acute form illness is sudden in onset with shaking chills high fever* and marked prostration often associated with vomiting and severe diarrhea Bacteremia occurs early and results in the development of widely disseminated *granulomatous abscesses The patient* passes into a state of stupor or coma and dies within 3 to 14 days In subacute cases the course of disease is similar except that the patient survives sufficiently long (3 to 4 weeks) for some of the disseminated *lesions to become clinically evident* These are likely to develop in the skin subcutaneous tissues muscles lungs bones liver and spleen Pyelonephritis orchitis epididymitis and prostatitis sometimes are seen A pustular rash has been observed *In rare cases melioidosis becomes chronic* with deep seated lesions and draining sinuses *which persist for years*

Diagnosis Cultural methods afford the best means of prompt diagnosis for *M pseudomallei* can be recovered readily from blood sputum exudates and urine As in glanders Strauss reaction can be elicited by intraperitoneal injection of infected material into male hamsters and guinea pigs The agglutination and complement fixation tests become positive after 2 to 4 weeks Biopsy specimens reveal characteristic pathologic changes indistinguishable from those seen in glanders

Treatment The reported fatality rate of 95 per cent attests to the inefficacy of older methods of treatment Experimental studies indicate that various sulfonamides oxytetracycline and chloramphenicol may be effective against the organism whereas it is resistant to penicillin streptomycin chlortetracycline and polymyxin Scattered reports indicate beneficial clinical results from the use of chloramphenicol chlortetracycline and various sulfonamides There evidently is wide variation in strain susceptibility so it is imperative that clinical treatment be controlled by in vitro sensitivity tests

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the ingestion of contaminated milk. The names *Haverhill fever* and *erythema arthriticum epidemicum* have been applied to cases in which there was no history of rat bite The clinical picture is the same in both types of infection.

Manifestations The incubation period is comparatively short The interval between the rat bite and the development of symptoms is usually 3 to 7 days while in the Haverhill epidemic the incubation period appeared to be only 1 to 3 days The onset of symptoms is sudden, with malaise and fever headache and vomiting About half the patients have one chill or more The temperature course is quite variable usually there is an intermittent or remittent type of fever Occasionally the fever is relapsing in type *Arthritis* usually appears during the first week of the disease and involves one or more of the larger joints which become hot swollen and tender In addition, there are generalized muscle aches A *skin eruption* appears in over 90 per cent of cases This is usually most prominent on the extremities in the vicinity of joints and consists of reddened flat papules 1 to 4 mm in diameter When infection has been acquired by rat bite there are usually signs of mild inflammation at the site and regional lymph nodes may be enlarged and tender

Bacterial endocarditis is a rare but serious complication of this infection

The natural duration of the disease is variable It may subside after a few days or it may persist for several weeks Recovery is the rule even without specific treatment and permanent disability due to joint involvement seldom occurs

Laboratory Findings A moderate leukocytosis with a leukocyte count of 10 000 to 15 000 is often observed although the leukocyte count remains normal in some cases A specific diagnosis is made by isolation of the causative organism from the blood or from joint fluid Growth is usually visible after 48 hr as small puffball" colonies at the bottom of the flask of liquid medium These show the characteristic pleomorphic configuration Agglutinins for *Streptobacillus moniliformis* can be demonstrated in the blood after the second week of disease

Differential Diagnosis In patients with a history of rat bite the principal difficulty is in differentiating *Streptobacillus moniliformis* from *Spirillum minus* infection. The clinical features of the two diseases may be very similar and positive diagnosis can be made only by demonstration of the causative organism in the patient s blood A tentative diagnosis of *Streptobacillus moniliformis* infection may be based on a short incubation period, prominence of joint symptoms and failure to respond to arsenical therapy Where there is no history of rat bite differentiation from such diseases as rheumatic fever chronic meningococcemia and malaria must be made

Treatment Penicillin is an effective agent in the treatment of *Streptobacillus moniliformis* infection A dose of 400 000 units a day should produce clinical improvement within 48 hr Treatment should be continued for about a week.

Prognosis This infection is always benign unless complicated by other illnesses

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134 BARTONELLOSIS

W Elizabeth Gambrell

Definition Bartonellosis or Carrion s disease is an infection with *Bartonella bacilliformis* a small pleomorphic bacillus found in close association with the red blood cells and transmitted by certain species of sandfly of the genus *Phlebotomus* Two well-defined clinical types may develop—an acute febrile anemia of rapid onset and high mortality designated *Oroya fever* and a benign eruptive form with cutaneous lesions of fairly long duration called *verruga peruana* Either of these types may be mild in some individuals with an asymptomatic invasion of erythrocytes by the organism These cases constitute the greatest epidemiologic hazard

Etiology *Bartonella bacilliformis* is a small motile pleomorphic gram negative bacillus which stains reddish violet with Giemsa s stain. It can be cultured on enriched media and chick embryos

Epidemiology The disease is limited geographically to certain valleys in the Andes chain of mountains in South America, comprising parts of Peru, Ecuador and Colombia It occurs in regions between the altitudes of 2 400 and 8 000 ft where the insect vector *Phlebotomus* propagates The reservoir of infection is not known, but certain plants and lower animals have been suspected since the disease is often contracted in regions which are practically uninhabited Epidemics occur more frequently during the rainy season and often co-

characterized by cyanosis dyspnea and hemoptysis and has been thought to result from inhalation of the spores It has not been established that this type of infection is dependent upon the pulmonary route of inoculation As has been mentioned human infection can occur from ingestion of the uncooked meat of infected animals However enormous numbers of organisms are probably necessary to produce the disease by this route in man and it does not occur in the United States

Laboratory Findings The serosanguineous fluid from the cutaneous lesion frequently contains many bacilli demonstrable by Gram s stain and culture Bacilli may be found on direct examination or culture of the blood of patients with bacteremia The blood leukocyte count is normal in mild cases but there is polymorphonuclear leukocytosis in severe disease Similarly the erythrocyte sedimentation rate may be increased but changes are irregular There are no characteristic abnormalities of the urine Patients with meningeal involvement usually show bloody spinal fluid in which the organisms are easily found by direct examination or culture

Diagnosis A positive diagnosis of anthrax can be made by isolation of the organism in culture However a history of occupational exposure and the characteristic eschar and edema should suggest the proper diagnosis Pyogenic infections of the skin are usually painful whereas the malignant pustule" is not. In addition cutaneous anthrax is rarely purulent The differential diagnosis of other diseases characterized by local ulceration at the portal of entry is discussed in Chap 128 (p 907)

Treatment and Prophylaxis Many antibiotics are effective in the treatment of human anthrax including penicillin chloramphenicol (Chloromycetin) tetracycline derivatives erythromycin and streptomycin Six hundred thousand units of aqueous crystalline or repository penicillin should be given once or twice daily until the local edema subsides The eschar goes through its natural evolution in spite of treatment and lymph node enlargement may persist for several days *Bacillus anthracis* cannot be recovered from the skin lesion after 24 to 48 hr of penicillin therapy but it may persist for a longer period when chloramphenicol or tetracycline is used

Exposure of personnel in industrial plants where contaminated animal products are handled still occurs in spite of measures to control it Sterilization of all raw wool mohair etc would probably remove this hazard but has had only limited application Transmission of anthrax from one human being to another has never been recognized Whereas the disease was fatal in 20 to 30 per cent of cases before specific antimicrobial drugs were available the mortality is now less than 1 per cent in the United States

A vaccine prepared from the protective" antigen of *B anthracis* is available but its effectiveness in man has not been fully evaluated Spore vaccines of various types are used with good effect in domestic animals in endemic areas

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133 *STREPTOBACILLUS MONILIFORMIS* INFECTION

Paul B Beeson

Definition This is an acute infectious disease caused by *Streptobacillus moniliformis* and characterized by fever arthritis and skin eruption When the mode of infection is the bite of a rat this disease is sometimes called *rat bite fever*

Etiology The causative organism is a pleomorphic microorganism which grows in chains with beadlike structures interposed It stains irregularly by Gram s method and is more easily demonstrated with Giemsa or Wayson methods This organism is regarded by some workers as a fungus because of its morphologic appearance and is sometimes called *Actinomyces muris* or *Streptothrix muris ratti* The L_1 pleuropneumonia like microorganism of Klieneberger has often been found in association with it but there is dispute as to whether the relationship between them is that of symbiosis or variation in morphology *Streptobacillus moniliformis* grows readily in liquid cultures enriched with blood or ascitic fluid The organism is pathogenic for mice in which it may cause acute polyarthritis

Epidemiology *Streptobacillus moniliformis* infection may be acquired in two different ways Nearly all sporadic cases result from the bites of rats These are most common in infants and children and in laboratory workers The other type of infection occurs in epidemics One such epidemic occurred in Haverhill Mass another in Chester Pa both were thought to have been caused by

uncommon Systemic complications of granuloma inguinale (such as invasion of the bones joints and viscera) have also been noted suggesting that the infecting agent can spread throughout the body by way of the blood stream

Clinical Manifestations The lesion of granuloma inguinale usually is a painless sharply demarcated ulcer having an exuberant red granulating base which bleeds easily on trauma The disease is extremely chronic and the ulcers slowly enlarge and coalesce Secondary infection frequently is present and produces a foul smelling seropurulent discharge Interference with lymphatic drainage may occur leading to swelling and elephantiasis of the genitalia similar to that caused by lymphogranuloma venereum When healing occurs further scarring and deformity may appear Lesions of the cervix of the uterus are frequent and sometimes are mistaken for carcinoma Lesions about the perianal area closely resemble condylomata lata of secondary syphilis and dark field examinations and serologic tests for syphilis are often necessary to differentiate the two conditions

The disease occasionally produces widespread manifestations such as arthritis and osteomyelitis In such instances there may be general debility anemia and malnutrition occasionally these have resulted in death

Diagnosis The diagnosis of granuloma inguinale is based upon demonstration of the presence of Donovan bodies Impression smears of early lesions stained by Wright s method usually will show Donovan bodies lying within the cytoplasm of large mononuclear cells The smear is of less value in chronic cases The diagnosis can also be made by histologic examination of fixed tissues The microscopic appearance of granuloma inguinale is essentially that of a richly vascularized granulation tissue with marked inflammatory cell infiltration Polymorphonuclear leukocytes are scattered throughout the tissue and form small microabscesses Numerous large mononuclear cells are also present and show finely reticulated or vacuolated cytoplasm Phagocytosis of polymorphonuclear leukocytes and other cellular debris by these cells is common Intracellular or extracellular Donovan bodies are readily seen in tissue sections particularly in acute cases In chronic cases they may be found only after considerable search but the histologic pattern is sufficiently characteristic to permit a tentative diagnosis even when organisms are not found Specific serologic tests (complement fixation) and skin tests have been developed but their diagnostic value is yet to be determined

Treatment Healing of granuloma inguinale will usually occur promptly following treatment with streptomycin chloramphenicol or the tetracyclines Streptomycin has the disadvantage of requiring parenteral administration The other antibiotics *seem to be more effective and are given orally* in doses of 2 Gm a day for approximately fifteen days These antibiotics have treponemicidal properties and should not be given until repeated dark field examinations and serologic tests have excluded the diagnosis of early syphilis

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136 *LISTERIA* AND *ERYSIPELOTHRIX* INFECTIONS

Paul D Hoeprich

History *Listeria* was isolated from a case of meningitis in 1918 but it was not recognized as a species until 1926 following isolation from a laboratory epizootic A succession of names followed until *Listeria monocytogenes* was accepted in 1940 Since then the many traits common to both *Listeria* and *Erysipelothrix* have led to the meritorious suggestion that but one generic name *Erysipelothrix* be used

Erysipelothrix infection in humans was described in 1884 when the name *erysipeloid* was advanced for the unique skin disease produced by this organism

Etiology *Listeria* and *Erysipelothrix* are gram positive nonsporulating microaerophilic bacilli *Listeria* is motile *Erysipelothrix* is not but neither can be identified solely on morphologic or cultural grounds Both organisms are readily and frequently confused with nontoxigenic *Corynebacteria* and occasionally with *Streptococci* Antigenic distinction is clearly drawn even to the point of distinguishing four types of *Listeria* unfortunately serums are not commonly available for laboratory diagnosis Accordingly suggestive morphologic and

incide with immigration of workers from uninfected areas

Manifestations The incubation period is approximately 3 weeks but may be longer The initial symptoms are fever and pains in the bones joints and muscles In the early stages the disease often resembles influenza or malaria but blood cultures for *Bartonella* are positive even in the absence of anemia Following this initial stage the patient develops in days or months one of the two classic types of the infection

Oroya Fever

This type is characterized by sudden onset of high fever extreme pallor weakness and a precipitous drop in the red blood cells The count may fall from normal to 1 million per milliliter in 4 or 5 days Muscle and joint pain is severe and headache insomnia delirium and coma are the terminal manifestations Death may occur within 10 days to 4 weeks Organisms are numerous in the blood and stained smears may show 90 per cent of the erythrocytes heavily invaded They are also present in the circulating monocytes and fixed phagocytes of the reticuloendothelial system Secondary bacterial infection particularly with *Salmonella* is an important factor in fatal cases Neither hemolysins nor agglutinins for *Bartonella* are found in the serum of patients Recovery results if the organisms decrease and fever abates The red cell count stabilizes then approaches normal values in about 6 weeks when convalescence begins

Verruga Peruana

This form of the disease characterized by a profuse skin eruption may follow the anemic form or may occur in patients without previous symptoms The verrugas vary in color from red to purple and vary in size and location They may be miliary nodular or eroding and they range in size from 2 to 10 mm up to 3 or 4 cm in diameter The three types of verrugas may occur together since eruption takes place in successive crops verrugas of all types and all stages of development may be found on the same patient The chief sites involved are the limbs and face and less frequently the genitalia scalp and mucosa of the mouth and pharynx They may persist from 1 month to 2 years The eruption is accompanied by pain fever and moderate anemia *Bartonella* may be demonstrated in the lesions and cultured from the blood

Treatment Recently antibiotics have proved very effective against the infection Results with penicillin in the anemic phase are spectacular but streptomycin has proved more efficacious in the eruptive phase Choramphenicol orally or intravenously is highly effective particularly when *Salmonella* infections are also present

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135 GRANULOMA INGUINALE

Albert Heyman

Definition Granuloma inguinale is a chronic ulcerative granulomatous disease usually confined to the skin and mucous membranes of the genito inguinal area but occasionally appearing in other portions of the body

Etiology The etiologic agent of this disease is the Donovan body a nonmotile gram negative bacillus In stained smears of the lesions the organisms appear as encapsulated bipolar bodies situated within large mononuclear cells In chick embryo cultures the morphology of the organism is variable and may consist of bipolar forms curved rods chains or unencapsulated bodies The organism is not pathogenic for laboratory animals and can be cultivated only in artificial media containing yolk material

Incidence Granuloma inguinale was once regarded as occurring only in tropical or subtropical areas but it has been shown to exist in almost every country and climate The majority of the cases in the United States are found in the Southeastern section usually among Negroes The incidence of the disease has decreased significantly in this country during recent years Approximately six hundred cases were reported in 1955

Pathogenesis Granuloma inguinale is generally believed to be acquired by sexual intercourse The disease is apparently not highly infectious however since it is frequently not transmitted to sexual partners The factors predisposing to invasion of the organism are not definitely known but the disease is found most frequently among sexually promiscuous individuals and in association with other venereal diseases The incubation period varies from 3 to 40 days Although the majority of infections appear on or near the external genitalia lesions about the face hands and neck are not

lating antibody disappears during the months following cure of *Listeria* infections There is no clinical evidence to indicate whether or not this augurs return to preinfection susceptibility With erysipeloid second attacks have been reported although these have been associated with different sources

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Section 7 Diseases Due to Toxin-producing Bacteria

137 DIPHTHERIA

Paul B Beeson

Definition Diphtheria is an acute infectious disease caused by *Corynebacterium diphtheriae* characterized by a local inflammatory lesion usually in the upper respiratory passages and by distant effects particularly on the heart and peripheral nerves due to specific exotoxin

History The first accurate description of the disease was given by Bretonneau in 1826 In 1883 Klebs described the morphologic appearance of *C diphtheriae* in stained preparations from diphtheritic membranes A year later Loeffler isolated the organism in pure culture and showed that it was capable of producing lesions resembling those of human diphtheria in experimental animals In 1888 Roux and Yersin showed that some of the manifestations of diphtheria in guinea pigs could be produced by sterile filtrates of *C diphtheriae* cultures By 1893 von Behring had demonstrated the neutralizing effect of antiserum on diphtheria toxin in experimental animals this was soon followed by the treatment of human diphtheria with antitoxin Schick described the skin test for susceptibility to diphtheria in 1913 Ramon in 1923 showed that the toxin could be altered in such a way as to render it noninjurious without destroying its antigenic property (toxoid) this was the basis for present methods of active immunization against diphtheria

Etiology *Corynebacterium diphtheriae* is a gram positive pleomorphic unevenly staining bacillus Three principal types are recognized *mitis intermedius* and *gravis* These types are distinguished by the appearance of their colonies on tellurite medium and by their capacity to ferment glycogen and dextrose European workers particularly those in the British Isles believe that there is a significant difference in the clinical manifestations of diphtheria produced by the different varieties gravis and intermedius diphtheria being associated with *severe toxic manifestations whereas the chief* danger of mitis diphtheria is laryngeal obstruction In the United States the gravis type is comparatively uncommon and less significance is attached to the relationship of the type of organism to the clinical form of the illness

The exotoxin produced by *C diphtheriae* is a potent poison having the chemical properties of a protein In highly purified preparations the minimum lethal dose for guinea pigs is as little as 0 0001 mg

Epidemiology Diphtheria can occur at any age but is most frequently encountered in children between the ages of two and five years There is no marked difference in sex incidence The principal mode of transmission is apparently by droplet infection especially from asymptomatic carriers Fomites probably play little part in the spread of diphtheria but *C diphtheriae* can remain alive and virulent in dust of a darkened room for several weeks This could serve as a means of spread of the infection It has been discovered that bacteriophage can effect a change whereby an avirulent form of *C diphtheriae* is converted to a virulent toxin producing form This may be of great significance in explaining the mysterious sudden appearance of virulent strains in populations previously free of them

Pathogenesis In the majority of cases the growth of diphtheria bacilli is confined to a superficial area there being little tendency for the organisms to invade deeper tissues or to enter the lymphatics or blood stream except in terminal stages of the disease The exotoxin produced by bacilli in the local lesion is however carried by the blood to all parts of the body Dissemination of this toxin with damage to remote areas appears to be greater

cultural data must be reinforced by demonstration of pathogenicity in animals

Swabbing the conjunctiva of the rabbit with *Listeria* regularly leads to a keratoconjunctivitis in 3 to 5 days The process usually remains localized to the eye and is caused by no other organism save rare strains of *Erysipelothrix* Generalized infection of the rabbit with either *Listeria* or *Erysipelothrix* provokes a monocytosis this reaction is more pronounced with *Listeria* Both organisms cause lethal disease on intraperitoneal inoculation of the mouse *Listeria* producing pinhead sized foci of hepatic necrosis *Erysipelothrix* giving rise to a severe conjunctivitis In general *Listeria* localizes in the meninges myocardium or liver *Erysipelothrix* lodges preferentially in skin endocardium or joints

Epidemiology and Pathogenesis Both organisms are widespread in nature where they appear to be primarily parasites causing disease in man and in a variety of birds and animals both wild and domestic It is presumed that wildlife comprises a major reservoir however a mechanism making for sporadic disease is obscure Infection in man is a dead end since transmission from human to human (except transplacental with *Listeria*) has never been proved The gastrointestinal tract has been postulated as the most likely route of entry for *Listeria*

Erysipelothrix apparently gains foothold through injuries to the skin and so is frequently an occupational disease The incidence of erysipeloid parallels the incidence of swine erysipelas in being highest in summer and early fall In this connection isolation of *Erysipelothrix* from flies may be pertinent

Manifestations Generally human disease caused by *Listeria* is not clinically unique *Listeria* however has recently been shown to be the cause of miliary granulomatosis Described as a pathologic entity in 1893 this disease was found in certain aborted premature stillborn and neonatal children Its onset in the mother may be entirely asymptomatic although more commonly a week to a month ante partum there has been malaise followed by a shaking chill perhaps associated with pains in the back or flanks The disease is benign and self limited in the mother and as these symptoms spontaneously disappear fetal movement diminishes or stops Infection of the fetus may take place as early as the fifth month of gestation delivery is normal though before term Fetal infection is usually lethal ante partum Of those children born alive most succumb within minutes post partum while the remainder usually do not survive beyond 2 weeks

Meningitis is by far the most common clinical form of human *Listeria* infection In a recent monograph Seeliger tabulated 291 cases of bacteriologically proved listerosis 87 involved the central nervous system Clinically meningitis due to *L monocytogenes* cannot be distinguished from meningitis due to other bacteria

Other syndromes caused by *Listeria* but exceedingly rare in occurrence include a generalized illness with high fever subacute bacterial endocarditis polyserositis and an oculoglandular disease

While *Erysipelothrix* may rarely cause endocarditis an intestinal and generalized disease in human beings *cutaneous infection is relatively common* Of 2 300 infected hands seen by King in a 4½ year period 115 were erysipeloid It is almost restricted to persons who in their occupations handle animals fish shellfish or materials derived from animals or dead matter of plant or animal origin Two to seven days after injury the typical lesion surrounds the site of entry This is a maculopapular nonvesiculated sharply defined purplish red zone which is accompanied by a feeling of heat burning irritation and pain There is some swelling and nearby joints become stiff By 3 to 5 days after injury centrifugal spread of the rash is definite Movement is slow and by 1 week the central portion of the lesion has healed and may be desquamating Local symptoms subside as healing occurs *There is no fever and general symptoms are uncommon* Regional lymphangitis and lymphadenitis nausea and vomiting rarely are seen

Laboratory Findings Both *Listeria* and *Erysipelothrix* grow well on the usual laboratory media Recognition of their significance when cultured usually depends on their being distinguished from diphtheroids Monocytosis is not commonly found Other laboratory findings are in keeping with the clinical syndromes engendered

Differential Diagnosis With the exception of miliary granulomatosis there is no clinical basis for singling out *Listeria* as cause of an infection Reports of diphtheroids or no pathogens in cultures from cases of clinical infection suggest *Listeria*

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Treatment Both *Listeria* and *Erysipelothrix* are susceptible to the action of penicillin the tetracyclines chloramphenicol erythromycin and novobiocin The agent of choice is penicillin General supportive measures should be used as indicated and local therapy such as drainage carried out as needed

Prognosis Prompt antibiotic therapy is highly effective On the basis of agglutinin titers circu

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Pathogenesis In the majority of cases the growth of diphtheria bacilli is confined to a superficial area there being little tendency for the organisms to invade deeper tissues or to enter the lymphatics or blood stream except in terminal stages of the disease The exotoxin produced by bacilli in the local lesion is however carried by the blood to all parts of the body Dissemination of this toxin with damage to remote areas appears to be greater

when the primary lesion is in the nasopharynx and less when it is in other sites such as the larynx or on the anterior nasal mucosa

The *primary lesion* of diphtheria is a superficial ulceration covered by a membrane It is most often located on the mucosal surface of the tonsils uvula soft palate nasopharynx nose larynx trachea or bronchi The membrane consists of a coherent mass of bacteria necrotic epithelium phagocytes and fibrin and is firmly attached to the underlying tissues The deeper tissues become intensely congested and edematous There is acute inflammation of the regional lymph nodes which are packed with phagocytes and necrotic material

In addition to the local lesion morphologic changes may be found in many tissues after death from diphtheria *Peripheral nerves* show degenerative changes in the medullary sheaths less commonly there is degeneration of the axis cylinders The *heart* is often dilated there may be cloudy swelling and hyaline changes in the myocardium Cloudy swelling is nearly always present in the *kidney* *Petechial hemorrhages* are occasionally found in the kidneys skin and adrenal glands

Death in diphtheria may result from respiratory obstruction due to the membrane and edema or it may be caused by the action of the toxin on the heart nervous tissue and other organs The mechanism of circulatory failure in diphtheria has been the subject of some controversy Unquestionably the myocardium often suffers damage In addition however some authorities believe that the toxin interferes with neuromuscular control of the peripheral circulation

The mode of action of this exotoxin seems fairly precisely defined It apparently acts as a respiratory enzyme for the parent bacillus When liberated in the tissues of an infected host it acts as a metabolic analog interfering with the host s cytochrome B system

Immunity The chief factor which governs susceptibility to clinical diphtheria is the presence or absence of antibody to the exotoxin This has been demonstrated unequivocally in experimental animals and is also supported by an impressive accumulation of observations on human beings

The *Schick test* is a rough method of determining the amount of antitoxin present in the circulating blood A standard quantity of diphtheria toxin in 0 1 ml fluid is injected intradermally and as a control an equal quantity of toxin previously heated to 70 C is injected into the opposite arm The result is read after 4 to 7 days A positive reaction is indicated by induration and erythema at the site of the toxin injection significantly greater than at the site of the control injection A negative test is indicated by absence of reaction or by reactions of equal intensity at the two test areas A negative Schick test can generally be interpreted as indicating a blood antitoxin level greater than 0 01 unit per milliliter of serum

Antitoxic immunity is not necessarily complete and individuals with a negative Schick test occasionally contract the disease especially if subjected to heavy exposure On the other hand many individuals with a positive Schick test escape diphtheria after being exposed Only about 50 per cent of adults in America are negative to the Schick test yet diphtheria is comparatively uncommon in adult life Furthermore second attacks of diphtheria are very rare despite the fact that only about 90 per cent of patients convalescent from the disease have become Schick negative The implication is therefore that factors other than antitoxic immunity play a part in determining susceptibility to clinical diphtheria There may be resistance to tissue invasion by the organisms themselves In general it may be said that a positive Shick test in a young child is strong evidence of susceptibility whereas in an older person the finding has less significance

Manifestations The incubation period is short usually 1 to 7 days and the early symptoms vary according to the location of the primary lesion

Faucial Diphtheria About half of all cases of diphtheria are of this variety The onset is insidious with slight soreness of the throat malaise and low grade fever gradually increasing in intensity during the next 2 or 3 days The patient usually appears quiet and does not complain excessively of sore throat The body temperature fluctuates between 100 and 102 F The blood pressure is normal and the pulse rate is moderately increased

The characteristic physical findings are in the throat The *diphtheritic membrane* may begin on one tonsil or both It is usually confluent and tends to spread to the adjacent pharyngeal mucosa often upward onto the soft palate and uvula Sometimes it extends across from one faucial area to the other There is little redness elsewhere so that the mucosa only a few millimeters away from the edge of the membrane usually appears normal At first the membrane is filmy or gelatinous but it soon becomes tough and coherent It may be gray yellow or white When an attempt is made to loosen it with an applicator there is bleeding of the underlying tissue When healing begins the membrane separates at the margins rolls up and breaks away in large pieces Therapy with antitoxin usually hastens the separation of the membrane and the return of the mucosa to normal appearance

Nasopharyngeal Diphtheria The membrane may spread from the faucial areas over the posterior pharyngeal wall up into the nasopharynx and even out into the anterior portion of the nose In such

instances the patient is always severely ill and subsequent development of toxic manifestations in the heart or nervous system is to be expected

In severe cases of faucial or nasopharyngeal diphtheria there are marked edema and swelling in the anterior and lateral parts of the neck in addition to enlargement of the regional lymph nodes This is sometimes referred to as "bull neck diphtheria and is generally the severest form of the disease

Anterior Nasal Diphtheria Lesions restricted to this area usually produce mild illness the chief symptom being persistent thin watery sometimes bloody nasal discharge which is irritating and gives the upper lip a raw appearance Toxic manifestations are rare

Laryngeal Diphtheria This may result from extension of nasopharyngeal diphtheria or the lesion may originate in the larynx The first symptom of laryngeal involvement is hoarseness As edema develops in the larynx or as the membrane increases in thickness or extends down into the trachea and bronchi there may be serious encroachment on the air passage Loose edges may flap into the lumen during one of the respiratory phases tending to cause valvelike obstruction Because of the small diameter of the larynx and trachea in young children the danger of respiratory obstruction is greatest in them A croupy stridor dilatation of the nares anxiety restlessness increased pulse rate sweating and flushing of the face are the early signs of obstruction Later there is retraction of the supraclavicular regions lower rib margins and the sternum with each inspiration and cyanosis is evident

Extrarespiratory Diphtheria Primary lesions occasionally develop in other parts of the body They may appear on the vulva or urethra or on wounds burns or chronic ulcers Wound diphtheria is a special problem in tropical areas and is one of the causes of "jungle sores These chronic ulcerated areas do not have a characteristic appearance diagnosis depends on cultural identification of *C diphtheriae* As a rule toxic manifestations especially those of the cardiovascular system are not prominent but peripheral neuritis may occur Healing of such lesions is speeded by administration of antitoxin

Cardiovascular System The frequency of cardiac involvement in diphtheria is illustrated by the fact that abnormal electrocardiograms can be demonstrated in about one half of all patients Various types of disturbance in rate and rhythm are observed The *pulse rate* may be rapid—130 to 170 per minute—or heart block may occur during the second and third weeks with the rate falling to 40 or 50 per minute The effects on the circulation are usually severest during the second week of illness The *blood pressure* tends to be low in some cases hypotension on the order of 70/40 persists for several days This is a grave prognostic sign Patients with severe cardiovascular involvement commonly exhibit marked pallor nausea and vomiting There may be gallop rhythm muffled heart sounds premature ventricular contractions or dropped beats When congestive failure becomes fully developed shortness of breath pain in the region of the liver and distention of the neck veins occur Death is the usual outcome in such cases Occasionally a patient in whom no previous manifestation of cardiac damage has been noted dies suddenly after some slight exertion it is presumed that there has been an acute disturbance in cardiac excitation with either ventricular fibrillation or ventricular standstill

Peripheral Neuritis Evidence of the neurologic complications is seldom observed before the second week of illness and may develop as late as the tenth or twelfth week The commonest initial sign of neural involvement is paralysis of the palate leading to difficulty in swallowing and regurgitation of fluids into the nose There is also a characteristic nasal quality in the voice Second in frequency is involvement of the third cranial nerve giving rise to extraocular paralysis or to impairment of ciliary function and difficulty in accommodation The seventh ninth and tenth cranial nerves may also be affected Less frequent and usually later in time is neuritis of the spinal nerves with paresthesias or weakness of the muscles of the abdomen neck or lower extremities Respiratory paralysis due to involvement of the intercostal and abdominal muscles is rare Loss of the patellar and Achilles tendon reflexes is occasionally seen These neurologic manifestations are not associated with pain but there may be paresthesias especially in the palms and soles Increased spinal fluid protein has been observed in a small proportion of cases of diphtheria and this in combination with postdiphtheritic neuritis may constitute a picture which closely resembles the Guillain Barre syndrome Symptoms of postdiphtheritic neuritis persist from a few days to several weeks usually they improve after the sixth week but instances have been reported in which disability persisted for several months Permanent sequelae however are virtually never encountered

Laboratory Aids Diagnosis by identification of *C diphtheriae* in stained smears from the membranous lesion is unreliable Nonpathogenic diphtheroid bacilli may lead to confusion or true diphtheria bacilli may not be detected A specific diagnosis depends on cultural demonstration of *C diphtheriae* In addition to routine throat cultures

on blood agar material swabbed from the membranous lesion should be inoculated onto Loeffler's and tellurite media Loeffler's medium provides *rapid presumptive diagnosis* organisms with characteristic morphology may be identified in smears from the culture after only 8 to 12 hr incubation For practical purposes this identification if made by a competent bacteriologist and if in conjunction with a compatible clinical picture is adequate Further identification if desired may be made *from the culture on tellurite medium which also* is of assistance in distinguishing the type of *C diphtheriae* Virulence tests need not be done on typical organisms isolated during the acute stage of the disease but they are indicated when the organism is cultured from the throat or nose of an asymptomatic or convalescent carrier

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Differential Diagnosis The differential diagnosis of lesions resembling faucial diphtheria is discussed in the section on streptococcal infections (p 852) Laryngeal diphtheria must be distinguished from "croup" and laryngotracheobronchitis due to *Hemophilus influenzae* or beta hemolytic streptococcus Croup usually comes on at night improves by morning and is without fever or local membrane In *laryngotracheobronchitis* there are high fever *leukocytosis and diffuse redness and edema of the* air passages usually associated with severe prostration and rapidly progressive respiratory obstruction *Foreign body in the nose* may resemble anterior nasal diphtheria

Complications *Purpura* occurs occasionally in cases with very severe toxemia *Streptococcal infection* is a frequent complication and may cause diffuse redness and edema of the palate and fauces with enlargement and unusual tenderness of the regional lymph nodes (This is one of the reasons why the throat culture should always be made with media suitable for both types of organisms) *Relapse* is extremely rare in diphtheria *Serum sickness* occurs in a variable proportion of patients convales*cent from the disease depending upon the amount* and kind of antitoxin which has been administered

Specific Treatment *Antitoxin* Every patient in whom the diagnosis of diphtheria appears probably should receive antitoxin without delay It is not justifiable to wait until the result of a culture is available The total dose of antitoxin should be given at once a second injection should never be necessary The dose required depends on the severity of the disease not on the age or body weight The severity of the disease is estimated on the basis of the extent of the membrane the amount of edema in the neck the pulse rate the blood pressure and the general appearance of the patient Patients with extensive nasopharyngeal or "bull neck" diphtheria should receive maximal doses In mild cases a dose of 20 000 units is adequate whereas in severe cases considerably larger quantities are needed Many authorities believe that no advantage can be derived from doses of *antitoxin in excess of 100 000 units although it is* the practice in some clinics to give as much as 200 000 units The antitoxin may be injected intramuscularly intravenously or by both routes In severe cases it is a good plan to give half the total dose intravenously and the remainder intramuscularly

Penicillin Therapy Most strains of *C diphtheriae* are sensitive to penicillin in vitro and the drug is employed generally in the treatment of diphtheria Evaluation of its effect has been difficult because of variability in the natural course of the disease and because physicians have been unwilling to withhold antitoxin therapy in order to assay the effectiveness of penicillin alone Certainly penicillin does not neutralize the exotoxin The general experience is however that penicillin therapy has been beneficial in a considerable proportion of the cases and should be used as a routine measure Throat cultures become negative earlier in patients who receive penicillin and the therapy is also of value in preventing or treating pyogenic compli*cations caused by streptococcal infection* A dose of 300 000 units daily for 10 or 12 days should be adequate

Treatment of Laryngeal Obstruction In laryngeal diphtheria death may result from obstruction of the air passages Management of this complication requires experience skill and judgment Patients with laryngeal diphtheria should be observed carefully for signs of obstruction described previously In mild cases some benefit may be afforded by having the patient breathe warm moist air from a steam kettle If obstruction becomes more marked it must be relieved either by intubation or by tracheotomy Intubation is the preferable method in an institution with experienced medical and *nursing staff in the hands of less experienced* personnel tracheotomy is probably the safer measure Where either of these procedures has been done special nurses should be on duty at all times since the tubes may suddenly become obstructed requiring removal cleansing or reinsertion It must be remembered that the patient is unable to call for assistance Tracheotomy or intubation has to *be maintained at least 3 or 4 days and occasionally* a tracheotomy tube is left in place for several weeks

One danger of this is that laryngeal stenosis may occur especially in cases where there has been secondary pyogenic infection around the site of the opening

General Management Isolation precautions should be observed Strict bed rest is indicated and physical effort should be reduced to a minimum during the acute stage as well as during early con valescence from diphtheria Soreness of the throat is usually moderate and swallowing not excessively painful hence local measures such as gargles and irrigations are not advisable as they may facilitate the absorption of toxin

A liquid or soft diet should be prescribed accord ing to the patient s preference Diet high in carbo hydrate and in vitamin C is usually advised but the basis for this has not been very well established If the patient receives an adequate caloric and fluid intake by mouth there is no reason for sup plementing the diet with parenteral feeding

The patient should be observed carefully for evidence of the effect of toxin on the cardiovascular system which is usually at its height during the second week of illness The pulse and blood pres sure should be recorded frequently In patients with hypotension it is common practice to raise the foot of the bed (This is also good procedure in indi viduals with palatal paralysis since it may help to prevent aspiration of material which collects in the throat) Numerous methods have been em ployed in combating heart failure in diphtheria but nothing seems of much benefit Digitalization is not helpful The hypotension can be alleviated by continuous administration of norepinephrine the value of this remains to be determined Intravenous administration of glucose solution is often advocated in treatment of patients with myocardial impair ment but there is no proof that this is beneficial There is no evidence that cortisone therapy reduces the damage caused by the toxin

Six weeks of bed rest is a minimum for patients convalescent from a severe attack of diphtheria In cases where there has been little evidence of toxe mia 2 or 3 weeks in bed is sufficient

Treatment of Carriers *Corynebacterium diph theriae* usually disappears from the throat between the second and fourth weeks but in a small propor tion of patients it may persist longer despite a second course of penicillin In such instances test for virulence of the organism is indicated if nega tive the patient need not be kept under isolation Tonsillectomy is effective in terminating the carrier state in some instances If these measures fail theoretically isolation should be maintained until the throat culture is negative but as a matter of fact experience suggests that after about 6 weeks patients seem to have less tendency to infect others and there is little danger in releasing them

Prophylaxis against Diphtheria Active immuni zation with diphtheria toxoid should be given to every child The first immunization should be carried out at about 6 months of age and the antitoxin response should be checked by a Schick test 6 months later If the child is still positive to the Schick test the course of immunization should be repeated It is advisable to give a booster dose at the time of beginning school, i e at five or six years of age

Active immunization of adults presents a more difficult problem because toxoid often causes severe local and general reactions in them Unless an indi vidual is very likely to be exposed to diphtheria toxoid injections are not indicated after the age of twelve If the decision is made to give toxoid to an adult the so called Moloney test for sensitivity can be employed One tenth milliliter fluid toxoid diluted 1 100 or 1 200 is injected intradermally If this provokes extensive erythema after 12 to 24 hr it is probable that injection of a standard im munizing dose will cause a severe reaction It is advisable then to defer further prophylactic meas ures and repeat the Schick test a few weeks later because these intradermal tests often provide anti genic stimulus sufficient to immunize the individual

Passive immunization is occasionally of value It may be given to the other children in a family or in a hospital ward where a case of diphtheria has developed A dose of 1 500 units of antitoxin can be expected to confer immunity for about 2 weeks

Prognosis The general fatality rate from diph theria varies in different parts of the world from 5 to 12 per cent The prognosis in individual cases is poor if there is extensive membrane with marked edema and lymphadenopathy The usual causes of death are laryngeal obstruction and circulatory failure

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mastication causes trismus and difficulty with chewing This highly characteristic phenomenon gives to the disease its common name of *lockjaw* Sustained contraction of the facial muscles produces a distorted grin called *risus sardonicus* Spasm of the pharyngeal muscles makes swallowing difficult Stiff neck and opisthotonos are also among the early signs Progressively other muscle groups become involved with tightness of the chest and rigidity of the abdominal wall the back and the limbs

The patient is conscious and mentally clear suffering great pain from muscular spasms There is profuse perspiration Fever may or may not be present The wound through which *Cl tetani* was introduced is usually evident although in 10 to 20 per cent of patients it cannot be found Neurologic examination discloses hyperactive tendon reflexes often with sustained clonus There are no sensory changes

The symptoms and signs increase in severity for several days Generalized tonic convulsions appear in all but the milder cases and are accompanied by spasm of the larynx and the respiratory muscles The resulting acute asphyxia may end fatally Convulsions are precipitated by various noxious stimuli such as a sudden noise a hypodermic injection or jostling of the bed If the patient survives the intensity of muscle spasm begins to diminish slowly during the second week Complete recovery may take several months

Occasionally *mild cases* occur in which there is only moderate muscle rigidity without tetanic seizures Sometimes the administration of tetanus antitoxin forestalls the development of generalized tetanus but not of *local tetanus* involving the muscles around the site of injury

Complications are frequent in tetanus Pulmonary atelectasis is common and may be followed by pneumonia which is especially to be dreaded for it seriously lessens the chances of recovery Constipation fecal impaction and urinary retention are often encountered Cystitis and pyelonephritis may develop in patients requiring catheterization Traumatic glossitis is seen frequently Compression fractures of vertebrae may result from the convulsive seizures Decubitus ulcers are likely to occur in patients under heavy sedation Serum sickness may appear 1 to 3 weeks after administration of antitoxin. Foot drop and muscle contractures may follow prolonged unconsciousness with the limbs in poor position Asphyxia from respiratory muscle or laryngeal spasm or from aspiration of secretions vomitus or food may be the immediate cause of death

Laboratory Findings The diagnosis of tetanus must be based on the clinical picture for laboratory examinations are of little assistance It is difficult to isolate the organism from the local lesion, and it is a laborious task to identify it precisely Furthermore the presence of *Cl tetani* in a wound does not necessarily indicate that the patient has tetanus The intoxication itself produces no change in the leukocyte count but leukocytosis may accompany secondary infection The cerebrospinal fluid is often under increased pressure but is otherwise not remarkable The urine is normal unless secondary urinary tract infection is present

Differential Diagnosis The incipient stages may resemble certain other conditions but fully developed tetanus is likely to be confused with few other diseases A frequent diagnostic problem is differentiation of *serum sickness* from early tetanus Many patients with injuries are given tetanus antitoxin and some subsequently develop serum sickness with temporomandibular arthralgia and trismus Usually arthralgia of other joints is also present together with urticaria and generalized adenitis Other conditions in which trismus occurs include *peritonsillar* abscess and local infections of the mouth and cervical region The finding of a normal spinal fluid in tetanus eliminates confusion with *meningitis* The clinical picture of *strychnine poisoning* with hyperexcitability of the muscles opisthotonos "risus sardonicus" and tonic convulsions may closely mimic tetanus except that the muscles are relaxed between seizures in strychnine intoxication while spasm tends to persist in tetanus In *rabies* inability to swallow is often an early symptom with drooling of saliva and spasms of the muscles of deglutition, followed by fever anxiety excitement delirium hyperesthesia, and convulsions A history of animal bite usually is obtainable

Treatment This is a grave disease for which unfortunately there is no specific treatment Nevertheless careful and constant attention to certain supportive measures often will change the outcome from death to recovery

Sedation A most important feature in therapy is the continuous use of sedatives in quantities sufficient to induce partial relaxation of muscle spasm and to prevent the dangerous acute tetanic seizure To accomplish this it sometimes becomes necessary to induce a state of unconsciousness yet one must avoid depression of respiration Various drugs have been used including barbiturates paraldehyde magnesium sulfate and tribromoethanol It is preferable to employ a combination of two drugs for example Sodium Amytal and tribromoethanol in an effort to minimize the toxic effects of each Sodium Amytal can be given orally subcutaneously or in an emergency intravenously in a dose of 0 25 to 0 5 Gm Tribromoethanol is administered *per rectum* in a dose of 15 to 30 mg per kg body weight Precise dosage schedules must be determined em

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Edward S Miller

Definition Tetanus is a severe intoxication characterized by generalized hypertonicity of skeletal muscles and convulsive seizures The manifestations result from the action of an exotoxin produced by *Clostridium tetani*

History Tetanus was described by Hippocrates and has been known since ancient times as a scourge of parturient women newborn babies and wounded soldiers As recently as the eighteenth century one out of every six infants born in the Rotunda Hospital in Dublin died of tetanus neonatorum The record was no more enviable in other parts of the world Studies beginning in 1884 demonstrated that the disease is caused by a toxin producing *Clostridium* In succeeding years immunologic methods were developed for the prevention of the disease

Etiologic Agent *Clostridium tetani* is a large motile spore forming gram positive bacillus without a capsule It is an obligate anaerobe and can be cultivated on artificial media in the absence of atmospheric oxygen Characteristic spherical terminal spores are produced which are highly resistant if protected from direct sunlight they can survive for many years Tetanus spores are often present in the intestinal contents of man and animals and have been found in soil and street dust in many parts of the world Under suitable conditions of growth *Cl tetani* elaborates a powerful exotoxin At least 10 antigenic types of the organism have been distinguished but differentiation is of no practical importance since the exotoxins of all have the same immunologic properties

The vegetative forms of *Cl tetani* and the exotoxin are destroyed by heating to 65 C for 10 min Spores can be killed by autoclaving it a temperature of 115 C for 20 min

Pathogenesis and Epidemiology The etiologic agent is carried into human tissues by contamination of a wound A variety of lesions both large and small may offer a suitable haven for growth lacerations compound fractures gunshot wounds burns frostbites bedsores and penetrating lesions produced by nails human and animal bites and slivers Cases have resulted from the use of unsterile surgical supplies and biologic materials Infections of the post partum uterus and the umbilical stump (tetanus neonatorum) were once extremely common but became rare after the introduction of aseptic obstetric techniques *Clostridium tetani* is so ubiquitous in the human environment that almost any contaminated wound may contain the organisms

The mere fact that *Cl tetani* is present does not necessarily mean that tetanus will develop local conditions in the wound must be suitable The organisms will proliferate only in the presence of an oxidation reduction potential far lower than that existing in normal living tissue Such a fall in potential may occur as a result of the presence in the wound of necrotic tissue soil cloth metal wood or of tetanus toxin Once the organism begins to grow it produces toxin and thereafter can itself maintain the conditions necessary for continued multiplication If the conditions for growth are not optimal tetanus spores may persist in the tissues for many months in a dormant but viable state Some may be carried by phagocytes to distant parts of the body If such tissues are later traumatized (as by surgical procedure) tetanus may then develop

Tetanus bacilli grow locally in a wound show little capacity to invade and are in themselves harmless They cause disease by virtue of a soluble exotoxin elaborated in the course of growth Actually two toxins are produced tetanolysin and tetanospasmin Tetanolysin has a lytic effect on red corpuscles in vitro and may also be damaging to leukocytes Its exact clinical effect is unknown but *it may contribute to tetanus infection by causing* local tissue necrosis and by antiphagocytic action Tetanospasmin is a protein substance with potent neurotoxic properties It is estimated that a dose of 0 13 mg is lethal for man The toxin acts at two points in the body on the neuromuscular end organs causing sustained muscle spasm and on the motor nerve cells of the spinal cord medulla and pons causing convulsive seizures Tetanospasmin has a strong affinity for nerve tissue of susceptible animals and when once combined with it in vivo cannot be neutralized by any amount of antitoxin The means by which toxin travels from the local lesion to the nervous system is still a matter of controversy According to one theory the toxin enters the neuromuscular end organs passes centripetally up the axones of motor nerves to the cord then spreads throughout the nervous system However other evidence makes it seem more likely that the toxin is carried to the nervous system via the circulating blood

Manifestations The incubation period varies from 2 days to several months but in two thirds of cases it falls within the range of 6 to 15 days Some patients have prodromal symptoms of restlessness and headache In others the first symptoms are those stemming from the developing muscular rigidity with vague discomfort in the jaws neck or lumbar region Among the first muscles to show involvement are those innervated by the cranial nerves particularly the fifth seventh ninth tenth eleventh and twelfth Spasm of the muscles of

in which antitoxin was given generalized allergic reactions occurred in 9 per cent of patients who had not had previous serum injections and in 24 per cent of those who had Furthermore patients who have had previous experience with horse serum often exhibit great acceleration in the rate of removal of antibody from the blood so that passive protection in them is short lived Another limitation to the use of antitoxin is the fact that not all who need it receive it In one-third to one half of cases of tetanus illness follows a wound so trivial that it is disregarded by the patient or is considered by the physician to be too insignificant to warrant antitoxin prophylaxis

Active immunization provides the most satisfactory type of prophylaxis A toxoid is used and initial immunization is achieved by giving two doses of an alum precipitated preparation or three doses of fluid toxoid at monthly intervals A booster dose is administered after 1 year and thereafter at intervals of 4 years A booster dose of fluid toxoid is likewise given immediately after an injury The antibody response to basic immunization is slow so that if active immunization is initiated at the time of injury the patient will not get the protection he needs However if he has previously received toxoid a satisfactory rise in serum antibody titer will occur within 4 to 6 days Ordinarily a booster dose after an injury may be relied on as late as 10 years after the last previous toxoid injection However there are occasional situations involving actively immunized individuals in which conservative judgment indicates the simultaneous administration of both antitoxin and toxoid (utilizing opposite arms) This should be done in massively contaminated large or multiple wounds particularly if they involve the head or neck It should also be done if there is doubt regarding previous active immunization or if there is delay in administering the booster

The foregoing discussion supports the proposition that all people should receive the benefit of routine active immunization Not only will this provide protection against tetanus but of even greater practical importance is the fact that it will obviate the frequent necessity of administering antitoxin with all the attendant hazards of sensitization A large pool of actively immunized individuals already exists in the United States including those who served in the armed forces and the many children who have benefited from pediatric immunization programs during the past 20 years Their immunity should not be permitted to wane It is particularly urgent that toxoid be administered to all patients who have allergies and to all who have received injections of horse serum In the latter group active immunization should be initiated 2 weeks after serum is given

Prognosis Case fatality rates are in the range of 30 to 40 per cent The outlook is especially grave in young children in the aged and in patients who develop pneumonia or other secondary infections It is worse if the incubation period is less than 7 days and if tetanal spasms supervene within 2 days after onset of other clinical signs Most deaths occur within the first 10 days of illness Survivors make a complete recovery Interestingly they are not immune to reinfection

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139 BOTULISM

Edward S Miller

Definition Botulism is an intoxication resulting from absorption of a poisonous substance produced by *Clostridium botulinum* The illness is characterized by generalized muscular weakness and frequently ends in death

History This disease was first described in Europe over 200 years ago It was sometimes seen in individuals who had eaten contaminated sausages For this reason the name of the illness is derived from the Latin word for sausage Outbreaks of botulism have been observed in the United States for many years chiefly in association with the consumption of inadequately processed canned foods

Etiology *Clostridium botulinum* is a motile gram positive bacillus which produces subterminal spores It grows readily on artificial media but only under anaerobic conditions The organisms are natural inhabitants of the soil and are found in abundance in many parts of the world In the United States the soils of the Rocky Mountain and the Pacific Coast regions are most heavily infested Organisms are frequently present on fruits and vegetables and thus are carried into the gastrointestinal tracts of animals and of man

pirically as indicated by the patient s condition It is often possible to reduce the amount of sedation required by gentle nursing care use of tracheotomy and administration of muscle relaxants as indicated below

Antiserum As soon as the patient has received adequate sedation he is given 100 000 units of antitoxin intramuscularly Hyaluronidase may be mixed with the serum to hasten absorption Serum never should be given intraspinally Prior to any surgical procedure 10 000 units may be infiltrated around the local lesion The usual tests for horse serum sensitivity must be performed beforehand This dose is sufficiently large to provide a safe excess of circulating antitoxin for 7 weeks or longer Repeated doses are not necessary except in unusual cases *involving extensive slow healing wounds* where readministration may have to be considered Antitoxin has no curative action in tetanus for it has no effect on the toxin which is already combined with nerve tissue Its only action is to neutralize newly formed toxin as it is produced in the lesion and before it has reached susceptible nerve cells

Treatment of Local Lesion The patient should receive sedatives and antiserum before the site of infection is manipulated The local lesion is then treated according to the same surgical principles that would be applicable if tetanus were not present Specifically a limb should not be amputated simply because the patient has tetanus

Nursing Care There is no disease in which meticulous gentle nursing care is of greater importance Constant attendance by special nurses is essential The patient should be in a quiet darkened room where all external stimuli such as noise drafts and jarring are kept to a minimum Secretions which accumulate in the pharynx must be removed by suction and postural drainage It has been shown that a 25 elevation of the foot of the bed is necessary to achieve successful postural drainage A padded tongue depressor should be placed between the teeth to prevent biting of the tongue during convulsions Bedsores can be avoided by use of a foam rubber mattress by changing the patient s position frequently and by special attention to care of the skin An indwelling catheter may be necessary because of persistent urinary retention Enemas should be given as needed to overcome constipation and prevent fecal impaction Foot drop and wrist drop can be prevented by suitable positioning with pillows sandbags or splints

Feeding Oral feeding usually is impossible because of trismus Intravenous feeding must be used during the most severe phase of illness and particularly in heavily sedated or unconscious patients It is best not to give fluids subcutaneously because the attendant pain stimulates the patient unduly In mild cases and in those who are recovering gavage is permissible utilizing a nasogastric tube of small caliber

Tracheotomy This simple surgical procedure has proved to be a safe and extremely valuable therapeutic adjunct in selected cases The successful application of tracheotomy in bulbar poliomyelitis has pointed the way to its wider use in other diseases such as tetanus in which airway obstruction often leads to anoxia pulmonary edema atelectasis and pneumonia The trachea can be suctioned easily and bronchoscopy can be employed when necessary Specific indications include spasm of the respiratory muscles laryngeal obstruction absent cough and swallowing reflexes excessive pharyngeal and tracheal secretions and coma In other words tracheotomy may be used to advantage in most moderately to severely ill patients Following tracheotomy it is often found that convulsive seizures are fewer and fewer sedatives are needed

Chemotherapy Penicillin is administered because of its curative effect on the tetanal infection itself

Muscle Relaxants Various agents of this type have been employed with varying degrees of success Curare is considered by many clinicians to be too dangerous because of the narrow margin between a relaxing dose and one which produces respiratory paralysis A depot form such as *d* tubocurarine in oil is somewhat less hazardous and longer lasting than the aqueous solution but should be used only when means of providing artificial respiration are at hand Mephenesin is somewhat less effective but is safer and therefore is perhaps a more satisfactory agent It can be administered intravenously as a 2 per cent solution in doses of 25 to 300 ml

Prophylaxis In the prevention of tetanus it is important that contaminated wounds receive thorough and prompt debridement Penicillin should be given because it has a definite effect in preventing or curing tetanal infection although it has no antitoxic properties In addition either active or *passive immunization is used to raise the resistance* of the patient

Immediate passive protection is achieved by administering horse serum antitoxin parenterally in a dose of 1 500 to 10 000 units depending on the extent of the lesion and the lapse of time between injury and treatment It acts by neutralizing free toxin and has no bactericidal effect Its use has been attended by great success only rarely does tetanus follow serum prophylaxis However there are serious disadvantages to its use It provides protection for only a week or two A significant proportion of patients exhibit allergic reactions including localized hypersensitivity serum sickness and rare but catastrophic anaphylactic shock In one large series

there may be hypersecretion of the lacrimal salivary and sweat glands but this is soon followed by diminished function Early in the illness excessive vagal tone sometimes causes the pulse rate to drop below 50 per minute Subsequently there are vagal depression and tachycardia Hypotension may occur as a result of peripheral vascular dilatation

The most significant physical alterations are seen in the nervous system Nearly all patients exhibit cranial nerve palsies involving any except the olfactory and optic nerves Weakness of the intrinsic and extrinsic eye muscles results in loss of the light and accommodation reflexes mydriasis ptosis strabismus diplopia or nystagmus The face becomes expressionless because of the seventh nerve paralysis Chewing swallowing and phonation are interfered with and the tongue cannot be controlled The neck muscles are unable to support the head The limbs become progressively weaker and movements may be incoordinated Complete paralysis of a limb is rarely encountered since death supervenes before this occurs Pulmonary ventilation is diminished as a result of weakness of the intercostal muscles and the diaphragm and cyanosis appears The superficial and deep reflexes are diminished but rarely absent The sensory system is intact

The paralysis may progress to a fatal termination after 2 to 10 days of illness Death results from paralysis of the respiratory muscles from obstruction of the airway or from attendant pulmonary infection In nonfatal cases the muscular weakness increases over a period of 10 days then almost imperceptibly function begins to return The muscles involved in respiration deglutition and speech are the first to show improvement Visual abnormalities persist for weeks or months Two to six months elapse before all symptoms disappear

Laboratory Findings The clinical diagnosis can be substantiated by identifying botulinus toxin either in the food or in the body of the patient A suspected specimen is suspended in saline solution and inoculated into mice If toxin is present the animals become paralyzed whereas control mice passively immunized with specific antiserum are protected The toxin can occasionally be demonstrated in the stomach or intestinal contents in the peripheral blood during life or in organ extracts after death Additional evidence may be gained by culturing *Cl botulinum* from the food although it must not be forgotten that the organism may be a harmless contaminant

The disease produces no characteristic changes in the leukocyte or erythrocyte counts in the urine or in the spinal fluid The electrocardiogram may show flattening of T waves and depression of S T segments

Differential Diagnosis Botulism may be confused with other diseases of toxic or infectious origin One should seek a history of recent consumption of home preserved foods and of coincident illness among other human beings or animals that shared the food Cranial nerve palsies and other paralytic phenomena are seen at times in poliomyelitis in viral encephalitis and in acute infectious polyneuritis These diseases are often accompanied by fever and by spinal fluid abnormalities In postdiphtheritic paralysis a history of preceding sore throat usually can be obtained The paralysis of shellfish poisoning appears a few minutes after ingestion of the sea food and is accompanied by paresthesia giddiness and somnolence In mushroom poisoning there are severe pains with marked vomiting and diarrhea Intoxication with the belladonna group of alkaloids leads to fever tachycardia and delirium An overdose of curare results in the rapid onset of widespread paralysis with death or recovery in the course of minutes or a few hours Myasthenia gravis is usually easily differentiated

Treatment and Prophylaxis Botulism is most satisfactorily controlled by prevention for methods of treatment are inadequate Practically all human cases are due to either type A or type B toxin and a bivalent antitoxin is available for prophylaxis and for therapy When the diagnosis is suspected on clinical grounds the antitoxin should be administered immediately by the intravenous route in a total dose of 100 000 units The antiserum will not reverse the effects of toxin which has already damaged the myoneural junction but it will neutralize that which has not yet been fixed by the receptor cells Early administration therefore is important The same dose should be given prophylactically to other individuals who have eaten the contaminated food but have not yet developed symptoms

The patient should be kept at strict bed rest There may be residual toxin in the gastrointestinal tract therefore it should be emptied by gastric lavage by enema and by catharsis Hypotension and shock can be counteracted by appropriate measures Careful and continuous nursing care is essential

Respiratory failure and airway obstruction are fundamental features which lead to death and every effort must be made to overcome these dangers The problems are similar to those encountered in poliomyelitis with respiratory paralysis Many of the newer therapeutic techniques which have proved successful in that disease are applicable to the treatment of botulism (see p 1076) When the swallowing reflex is lost oral feeding becomes dangerous and must be replaced by nasogastric tube or intravenous feeding Pharyngeal secretions are removed by suction and by postural drainage The patient should be placed in a mechanical respirator with the first signs of weakness of the

This organism produces an extremely potent exotoxin (called *botulin*) *under suitable conditions* of anaerobic growth in a variety of foodstuffs of animal and plant origin There are five different immunologic varieties of *Cl botulinum* designated as types A B C D and E They differ in that each produces a specific exotoxin which is antigenically distinct from the others These toxins are by far the most potent poisons known Type A toxin has been isolated in pure crystalline form and identified as a globulin with a molecular weight of approximately 1 000 000 Type B toxin has likewise been purified and found to possess a molecular weight of 60 000 There are no qualitative differences in the effects of the different types of toxins but there are marked species differences in host susceptibility Human cases are usually due to types A and B and rarely to E only one case of type C has been reported and none of type D

Some spores can withstand boiling for as long as 22 hr but are killed by moist heat at 120 C in 4 to 20 min The exotoxin is more labile and is inactivated by boiling for 10 min

Pathogenesis Botulism occurs as a result of the ingestion of toxin which has previously been formed in food The botulinus bacillus does not produce toxin in the alimentary tract and therefore is harmless when ingested This organism frequently contaminates foodstuffs but no human disease has resulted from the consumption of fresh food However the spores will survive and produce toxin if improper methods of food preservation are employed The products implicated are canned fruits and vegetables and canned or preserved fish and meats as well as cheeses Commercial packers in *this country now use sterilizing techniques which* are adequate to destroy all spores The chief danger lies in home canned products particularly when high pressure steam methods are not utilized Because of this most outbreaks in the United States have occurred in individual families or other small groups About fifteen such outbreaks are reported annually in this country the majority of them in California Washington and Colorado

Spoilage of food may be suspected because of abnormal taste odor gas turbidity or softening but there may be no observable alterations Therefore when possible home preserved products *should be boiled for 10 min before use* Needless to say any item which appears to be spoiled must be destroyed without being tasted Care must be taken to prevent contact of contaminated food with cuts on the hands for a dangerous quantity of botulin might conceivably be absorbed

The natural and usual portal of entry of botulin is via the gastrointestinal tract The toxin is a protein yet it resists digestion It is absorbed intact from the small *intestine* and possibly also from the stomach but poorly from the colon Until recently *it was believed that this represented the only nat*ural means by which human beings acquire botulism though it has long been known experimentally that animals are far more susceptible to botulin *administered parenterally than to that re*ceived via the oral route It is therefore of interest to note several recent reports which indicate that *Cl botulinum* can sometimes proliferate in contaminated wounds produce toxin and thus cause clinical botulism in man This is an entirely new concept of pathogenesis and demands a careful evaluation of the course of illness in patients with wound infections particularly in the presence of gas gangrene

Botulinus toxin exerts a highly specialized biochemical effect acting only on nerve cells The principal and probably the only sites of action are at the myoneural junctions and at parasympathetic nerve endings It has no effect on the central nervous system it does not abolish conduction in the nerve itself it does not affect the reactivity of the end plate *nor is there any firm evidence of effect* on muscle The toxic effect pertains to acetylcholine either in inhibiting its synthesis or in preventing its release from the terminal fibers

Botulism is not limited to man The natural disease occurs in a varied assortment of wild and domesticated animals and birds while still others are susceptible to experimental inoculation The disease is sometimes seen in chickens or cats in relation to human outbreaks when these animals are fed scraps from the table

Manifestations Following ingestion of botulin there is a latent period usually in the range of *12 to 36 hr though it may be as short as 2 hr or as* long as 14 days The incubation period is shortened and the severity of illness increased as the size of the dose is increased

Illness begins insidiously with fatigue weakness headache and dizziness Digestive complaints are observed in only one third of cases and probably are due to local irritation from other substances in the spoiled food rather than to the toxin They consist of nausea vomiting upper abdominal discomfort and diarrhea Such symptoms subside after a few hours and thereafter there is obstipation with abdominal distention but without tenderness *or pain Botulism is essentially a generalized para*lytic disease and these manifestations soon dominate the clinical picture Weakness is noted during the first 24 hr in the muscles innervated by the cranial nerves Soon it spreads to the rest of the skeletal system Except for headache botulism does not give rise to pain

The patient is clear mentally and remains so throughout the course of his illness There is no fever unless secondary infection occurs Initially

injected into undamaged tissues of experimental animals The nature and the amounts of toxin produced vary considerably for different species and strains *Clostridium welchii* elaborates alpha toxin a lecithinase which is the principal tissue-destroying hemolytic and "lethal" toxin Other *Cl welchii* toxins include collagenase hyaluronidase hemolytic theta toxin a substance that damages vascular endothelium and a factor that inhibits leukocyte migration and phagocytosis None of these organisms produces a neurotoxin muscle spasm or paralysis in a patient with gas gangrene indicates concurrent tetanus or botulism

Gas Gangrene (Clostridial Myonecrosis)

Gas gangrene occurs as a complication of extensive injury to skeletal muscle The incubation period is usually 1 to 4 days but may vary from 6 hr to 6 weeks or longer The earliest symptom is sudden severe pain in the injured part The distal portion of an involved limb becomes cold and edematous within a few hours and eventually pulseless and gangrenous The wound drains a watery brown material with a characteristic sweet foul odor The surrounding skin is usually dusky brown or reddish and vesicles or hemorrhagic bullae may develop particularly in *Cl septicum* infections Gas is usually not detectable in the tissues by palpation but tiny bubbles may be seen in the discharge from the wound The involved muscle appears dark red or black herniates through the wound and sloughs at the surface

Systemic manifestations developing shortly after onset of severe pain and swelling of an injured extremity strongly suggest gas gangrene The patient is prostrated pale and motionless but is usually well oriented alert and extremely apprehensive The temperature usually does not exceed 101 F and may be normal As the illness progresses there may be anorexia vomiting profuse watery or bloody diarrhea and eventually circulatory collapse with clammy skin tachycardia hypotension and sometimes wide pulse pressure and dicrotic pulse Intravascular hemolysis is rare with *Cl welchii* myositis Pericardial effusion is sometimes noted Delirium and coma may precede death but more commonly the patient dies suddenly several days after onset often during surgery or anesthesia or while only being moved Acute renal failure is occasionally a late complication

Gas gangrene must be differentiated from nonclostridial infections of gangrenous limbs caused by anaerobic streptococci (p 869) or aerobic gas forming coliform bacilli (p 879)

Clostridial Cellulitis

This is a relatively benign infection of the skin and subcutaneous tissues that occurs in approximately 5 per cent of wounds contaminated with pathogenic clostridia The disease is characterized by spreading necrosis of superficial tissues and a profuse foul smelling brown seropurulent exudate Gas which crepitates on palpation invariably forms in the subcutaneous tissues and may involve an entire limb or form a localized gas abscess In clostridial cellulitis the underlying skeletal muscle is not involved pain is not severe and the only systemic manifestations are slight fever and moderate tachycardia It can usually be differentiated from streptococcal cellulitis by the presence of subcutaneous gas and the absence of erythema

Postabortal and Puerperal Sepsis

Uterine infections with *Cl welchii* usually occur after incomplete abortions induced under unsterile conditions and rarely after spontaneous abortions or prolonged labor at term The organisms presumably invade the damaged endometrium through the retained products of conception The earliest symptoms are caused by instrumentation and consist of metrorrhagia suprapubic and back pain chills and fever Fever of 100 to 103 F often with chills usually recurs several days after abortion but the incubation period can be as short as 6 hr Vaginal bleeding is almost invariably present and there is often a brown foul smelling vaginal discharge containing necrotic tissue The cervix is soft and patulous and the uterus and adnexae are usually very tender The lower abdominal wall is often tense or signs of generalized peritonitis may be present secondary to perforation of the uterus or parametrial extension of infection Nausea vomiting and profuse diarrhea are often prominent Unusual local complications of the uterine infection are gas gangrene of the vagina and rectum with formation of a cloaca and clostridial cellulitis of the anterior abdominal wall following cesarian section or hysterectomy At times the infectious process is confined to the endometrium and myometrium with intrauterine gas formation (physometra)

Systemic manifestations usually appear with dramatic suddenness As in gas gangrene the clinical picture is dominated by circulatory collapse with hypotension extreme tachycardia cyanosis hyperpnea and pulmonary edema Despite severe prostration the patient is well oriented alert and apprehensive almost to the end Massive intravascular hemolysis accompanied by hemoglobinemia hemoglobinuria and jaundice is often the most striking feature of the disease Death may occur a few hours after onset or be delayed for several days Patients who recover from the acute episode of shock dehydration and hemolysis frequently develop acute renal failure

Diseases to be considered in the *differential diagnosis* include perforated uterus ruptured ectopic

respiratory muscles Tracheotomy is an essential part of the program providing an unobstructed air way and a means of removing tracheal secretions

Narcotics sedatives and other respiratory depressants are strictly contraindicated even though patients are often apprehensive and restless

Effective toxoids have been developed for protection against both types A and B toxins They are useful chiefly in protecting laboratory workers

Prognosis The fatality rate in type A cases is 70 per cent while in type B cases it is 20 per cent or less If a patient survives the first 10 days of illness his chances of recovery are good Convalescence may take as long as 6 months but it leads eventually to complete restoration of function

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140 OTHER CLOSTRIDIAL INFECTIONS

Edward W Hook and Robert R Wagner

Introduction and History Bacteria of the genus *Clostridium* are normal inhabitants of soil and the gastrointestinal tract of man and animals Most of the 50 species that have been recognized are saprophytic but others are infectious for man and animals usually under conditions of lowered host and tissue resistance Infections with these organisms are often associated with profound systemic manifestations and all pathogenic clostridia except *Clostridium tetani* (p 924) and *Cl botulinum* (p 927) are capable of causing extensive tissue destruction at the site of invasion Diseases caused by these other clostridia include gas gangrene cellulitis postabortal and puerperal sepsis and rarely pleurisy peritonitis or meningitis In addition ingestion of food contaminated with certain clostridia may cause enterocolitis without the neurologic manifestations of botulism

Hippocrates and Celsus were aware of the relationship between penetrating wounds and gas gangrene but the nature of this disorder was not appreciated until the discovery of pathogenic clostridia by Pasteur Novy and Welch The incidence of gas gangrene diminished markedly with the advent of antiseptic surgery in the latter half of the nineteenth century only to rise again to epidemic proportions during the trench warfare of the First World War The rarity of serious clostridial infections in United Nations troops in Korea attests to the advances in surgical management of war wounds Gas gangrene and clostridial cellulitis are still encountered in neglected civilian injuries and clostridial infections of the uterus account for a large proportion of deaths from criminal abortions

Etiology Wounds complicated by gas gangrene usually contain a mixture of pathogenic and saprophytic clostridia often including *Cl tetani* as well as a variety of other organisms *Clostridium welchii (perfringens) Cl oedematiens (novyi)* or *Cl septicum* (vibrion septique) can be cultured from most cases of gas gangrene and clostridial cellulitis and *Cl welchii* causes virtually all clostridial infections of the uterus *Clostridium bifermentans Cl sporogenes Cl histolyticum* and *Cl fallax* are less virulent organisms that occasionally cause gas gangrene but are more commonly associated with localized cellulitis *Clostridium botulinum* has also been isolated from wound infections of several patients with clinical manifestations of botulism (see p 928)

The clostridia of gas gangrene and related infections are anaerobic or microaerophilic gram positive bacilli that produce abundant gas in artificial media and form subterminal endospores *Clostridium welchii* is encapsulated and nonmotile rarely sporulates in artificial media and its spores can be destroyed by boiling

Epidemiology and Pathogenesis Clostridia do not penetrate intact skin or mucous membranes but gain entrance to the tissues through penetrating wounds or perforated abdominal viscera Gas gangrene develops only in devitalized tissues in which the arterial circulation has been compromised by trauma constricting tourniquets or casts or by obliterative arterial disease Infection is most frequent after severe muscle injuries particularly of the thigh and is more common in wounds complicated by compound fractures or lodgment of foreign bodies

Gas gangrene and related infections are characterized by extensive necrotizing myositis edema thrombosis of small vessels interstitial gas bubbles and minimal infiltration of leukocytes Although bacteremia may occur infection at distant sites is rare Clostridia produce potent exotoxins during the course of infection spores or vegetative forms washed free of toxin are completely innocuous when

Section 8 Mycobacterial Infections

141 TUBERCULOSIS

William M M Kirby

Definition Tuberculosis is an infectious disease of protean manifestations which is widespread among man and animals The initial lesion is usually located in the lung and from it tubercle bacilli may spread by intrabronchial dissemination or by direct extension or they may be carried in the blood stream to many organs throughout the body causing destructive lesions at the time of dissemination or after long periods of latency In the majority of individuals the primary infection becomes arrested but it causes alterations in the immunologic state of the host which modify the response of the tissues to subsequent reinfection or to exacerbation of the primary infection Pathologically varying degrees of exudation production tubercle formation necrosis and fibrosis are observed depending on the organ involved the number of infecting bacilli the virulence of the organisms and the immunologic state of the patient

History The discovery of lesions involving the bones of a Neolithic man and of Egyptian mummies indicates that man has been afflicted with tuberculosis during much of his evolutionary development The contagiousness of tuberculosis was recognized by Aristotle and the name *phthisis* was conferred by Hippocrates because of the marked bodily wasting produced by the disease An important advance occurred in 1819 when Laennec asserted in his treatise on the use of the stethoscope that tubercles wherever present were manifestations of a single disease process This disputed doctrine was supported by the inoculation experiments of Villemin in 1865 and was finally proved by the discovery of the tubercle bacillus by Koch in 1882 Subdivision of the tubercle bacilli pathogenic for man into three types followed the avian bacillus being isolated by Maguccı in 1890 and human and bovine types being differentiated by Theobald Smith in 1898

A most important development in the history of tuberculosis was the discovery of streptomycin by Waksman and his associates in 1944 The early studies of Hinshaw and Feldman indicated that streptomycin possessed therapeutic potentialities unapproached by earlier chemotherapeutic agents Lehmann working with derivatives of benzoic acid was responsible in 1943 for experiments leading to the synthesis and eventual clinical utilization of para aminosalicylic acid Isoniazid was discovered independently in 1951 by three groups of chemists who were studying the tuberculostatic action of derivatives of nicotinic acid

Prevalence and Incidence Tuberculin surveys and autopsy studies 50 years ago indicated that virtually 100 per cent of the population was infected prior to the age of twenty The situation has changed greatly since that time in the United States for example tuberculin surveys now reveal only 20 per cent of positive reactors in young adults and it is estimated that less than 50 per cent of the total population is infected Skin hypersensitivity is known to disappear in a certain percentage of individuals and consequently autopsy studies yield higher figures than tuberculin surveys Autopsies performed by Medlar in New York City from 1944 to 1946 showed that the incidence of infection in individuals over fifty years of age was above 80 per cent These studies indicate that the decline in the incidence of infection has occurred chiefly among the younger age groups

The *morbidity*—i e the frequency of actual tuberculous disease—is difficult to estimate accurately but most authorities agreed that there were approximately 350 000 active cases in the United States in 1957 Thus although almost half the total population was infected by the tubercle bacillus clinically significant disease develops in only a relatively small number of individuals

There has been a striking decline in the *mortality rate* from tuberculosis during the past 50 years From first place in 1900 with over 200 deaths per 100 000 population tuberculosis by 1940 had fallen to seventh place as a leading cause of death with a mortality rate of 45 9 per 100 000 By 1950 the figure had fallen to only 22 and in 1954 it was 10 The most important factors in this decline have been the improvement in living standards with better nutrition and housing shorter working hours and earlier diagnosis and treatment Tuberculosis remains one of the major causes of death in young adults ranking fourth in the age group fifteen to thirty four

Since 1945 the mortality rate has declined more precipitously than during the preceding two decades because of the advent of chemotherapy From 1938 through 1945 the death rate declined about 3 per cent each year From 1946 through 1951 the average annual decline increased to 11 per cent and in 1952 (when isoniazid was introduced) through 1954 it was 20 per cent

Unfortunately there has not been a proportionate decrease in the number of newly discovered active infections Since 1930 for example the

pregnancy ingestion of toxic abortifacients streptococcal or staphylococcal puerperal sepsis pelvic thrombophlebitis with septic pulmonary emboli acute hepatic necrosis of pregnancy sickle cell crisis and Weil s disease

Clostridial Infections of Serous Surfaces

Pathogenic clostridia are occasionally introduced into the abdomen thoracic cavity or cranium through penetrating wounds or surgical incisions Actual visceral infections with these organisms are exceedingly rare and almost invariably associated with a mixed bacterial flora Clostridial pleurisy may involve the underlying lung but is usually an *indolent localized infection with minimal systemic* manifestations Clostridial meningitis is often associated with a necrotizing cerebritis Clostridial peritonitis may follow perforation of the gallbladder appendix or other viscus and is usually rapidly fatal Necrotizing hepatitis caused by *Cl oedematiens* has been described

Clostridium welchii Food Poisoning

Meat and meat products contaminated with *Cl welchii* have been responsible for outbreaks of acute gastroenteritis Nausea vomiting abdominal cramps and diarrhea occur 8 to 12 hr after ingestion of the incriminated food and persist for 12 hr or less Systemic manifestations are usually absent and recovery is uneventful in most outbreaks although a severe form of the disease in Germany known as enteritis necrotans has been *associated with a high incidence of intestinal ob*struction severe dehydration shock and death The intestinal flora is not significantly altered and attempts to demonstrate specific toxins by feeding clostridial cultures to human volunteers have not been uniformly successful

Laboratory Findings The diagnosis of gas gangrene clostridial cellulitis postabortal sepsis or other clostridial infections is based primarily on clinical criteria Smears of wound exudate or uterine scrapings may show abundant gram positive *bacteria as well as other organisms Thioglycollate* broth deep meat broth and blood agar plates incubated in an anaerobic jar should be inoculated for definitive identification of specific clostridia However *interpretation of positive wound cultures is* difficult because clostridia are frequent contaminants *Clostridium welchii* septicemia and bacilluria are common in postabortal infections but rare in gas gangrene and other clostridial infections All attempts to demonstrate circulating toxins have been unsuccessful

Polymorphonuclear leukocytosis occurs frequently in gas gangrene and invariably in post abortal sepsis total blood leukocyte counts occasionally *exceed 60 000 cells per cubic millimeter* Marked thrombocytopenia has been described in clostridial sepsis X ray examination sometimes reveals the presence of gas in the muscles subcutaneous tissues or uterus The urine frequently contains protein and casts Renal insufficiency may lead to severe and irreversible azotemia hyperpotassemia hyperphosphatemia and acidosis

Profound alterations of circulating erythrocytes are common in postabortal sepsis but rare in other clostridial infections Hemolysis results in severe *anemia hemoglobinemia hemoglobinuria and ele*vated levels of indirect serum bilirubin Spherocytosis increased osmotic and mechanical fragility of the red blood cells erythrophagocytosis and methemoglobinemia have also been described

Treatment Serious clostridial infections require prompt surgical intervention Early debridement or amputation of the involved extremity may afford dramatic relief of the systemic manifestations of gas gangrene Curettage of the uterus should be performed for diagnosis and treatment of post *abortal clostridial infections Hysterectomy probably* does not alter the course of the disease Simple excision and adequate drainage usually suffice for treating clostridial cellulitis Penicillin is the antibiotic of choice for all clostridial infections and should be administered in doses of at least 20 million units a day Despite the fact that clostridial toxins are rapidly fixed in the tissues and cannot be demonstrated in the blood early treatment with antitoxin appears to reduce the mortality from gas gangrene complicating war wounds It is recom*mended that 50 000 units of polyvalent gas gan*grene antitoxin be given every 4 to 6 hr to all patients with suspected gas gangrene or clostridial postabortal sepsis The use of clostridial toxoids for prophylactic immunization of individuals in hazardous occupations awaits evaluation

Intravenous infusions of blood plasma volume expanders fluids and electrolytes are often required to combat shock anemia and dehydration Renal insufficiency should be treated in the same manner as acute tubular necrosis from other causes (see *p 1367*)

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contact with infected material Tuberculous food handlers for example may deposit organisms on food or eating utensils which are then placed in the mouths of uninfected subjects Similarly tuberculous sinuses and urine and feces may occasionally be sources of infection Kissing is an example of transmission by direct contact and is probably an important source of infection in infants Dogs are susceptible to both the human and the bovine bacillus and may occasionally transmit tuberculosis Cats are said to be highly resistant to the human type of bacillus but susceptible to the bovine form Placental transmission of tuberculosis in the human occurs but is rare

The various sources of infection described above apply chiefly to the human bacillus which is responsible for over 95 per cent of tuberculous infections in this country The intensive campaign to destroy tuberculous cattle and to encourage pasteurization of milk has practically eliminated the milk borne bovine type of tuberculosis in the United States In some countries ingestion of contaminated milk is still responsible for a large number of cases of cervical adenitis and abdominal tuberculosis in infants and children Infection of the lungs by the bovine bacillus is uncommon even in areas in which it is responsible for a high incidence of intestinal tuberculosis The tubercle bacillus is destroyed by boiling in water for 2 min or by pasteurization at 60 C for 20 min

PATHOLOGIC ANATOMY

This subject is considered exhaustively in text books of pathology a brief summary will provide adequate reorientation for the purposes of this discussion In general two types of tissue response predominate in tuberculosis—exudative and productive According to Pinner exudative reactions tend to occur in association with loose tissue structure large doses of highly virulent organisms and bronchogenic spread to parenchymal tissues Productive reactions are commonly observed with small doses low virulence and firm tissue structure and in lesions in interstitial tissues resulting from hematogenous dissemination

In the exudative lesion in the lung polymorphonuclear leukocytes large mononuclear cells and fibrin infiltrate the alveolar spaces After a variable period of time this pneumonic type of lesion may undergo partial or complete resorption or it may caseate If caseation occurs areas of caseous pneumonia become liquefied a process which leads to cavitation with leukocytes and exudative material being expelled as sputum Caseous areas may also be replaced gradually by fibrosis and calcification It should be emphasized that the exudative reaction may be misdiagnosed easily even by histologic examination since epithelioid cells Langhans giant cells and caseation may be absent

The productive lesion or *tubercle* involves growth of new granulation tissue supported by a definite reticulum which pushes the normal tissue aside The tubercle consists of Langhans giant cells epithelioid cells and a surrounding layer of lymphocytes Later the granulation tissue making up the tubercle forms a fibrous capsule around the periphery differing in this respect from the exudative lesion in which the surrounding fibrosis is produced by collagenous tissue normally present in the peribronchial perivascular and septal spaces Productive lesions rarely undergo resolution to the extent observed with exudative lesions

Rarely primary tissue necrosis may occur in tuberculous infection This is observed in the so called acute caseating miliary tuberculosis and presumably results from the sudden hematogenous dissemination of large numbers of tubercle bacilli in extremely hypersensitive individuals

IMMUNITY

Native Resistance Man possesses a relatively high degree of native resistance to tuberculosis as manifested by his ability to arrest the infection in the great majority of instances Susceptible animals such as the guinea pig have little resistance and almost invariably succumb to the disease There are probably no differences in actual native resistance among white races the higher mortality rate of city-dwelling Irish as compared with Jews is probably due to natural selection of resistant individuals among the latter Negroes and Indians possess distinctly lower native resistance than whites Resistance is influenced by age and sex examples are the high mortality rate in infants and in females during the child bearing period The effect of environmental influences such as poor nutrition and overcrowding is clearly demonstrated by the close correlation of tuberculous mortality with economic and hygienic alterations during war time

Acquired Resistance Koch observed that cutaneously inoculated guinea pigs developed an indolent ulcer at the local site with rapid spread to and marked enlargement of the regional lymph nodes and eventual death from generalized tuberculosis In contrast animals previously infected developed an intense local skin reaction within a day or two followed by ulceration and healing Spread from the local site was greatly inhibited and there was little involvement and enlargement of the tributary lymph nodes Subsequent studies have confirmed and elucidated the chief characteristics of the lesion of reinfection in animals and man namely (1) an intense local inflammatory

death rate has fallen from 70 to 10 per 100 000 persons while the new case rate has declined only from 100 to 60 Thus the situation has reached the point where the mortality rate is no longer an accurate index of the prevalence of tuberculous infection The large number of new cases discovered each year (over 75 000) indicates that many individuals with undiagnosed active tuberculosis are still at large in the community Of the estimated 350 000 cases of active tuberculosis in the United States today 125 000 remain unrecognized

The tendency for tuberculosis to occur among older age groups deserves special mention In only 20 years the percentage of newly discovered cases in individuals under the age of thirty has dropped from more than 50 per cent to 20 per cent During the same period the percentage of patients in tuberculosis hospitals who are over sixty years of age has increased from 6 to almost 25 The rate of newly reported active cases of tuberculosis among men is nearly twice that among women in patients over fifty years of age the ratio is 4 1 Homeless alcoholic men make up a large proportion of the new cases

ETIOLOGY

Three types of tubercle bacilli—human bovine and avian—are known to infect man The last is of least importance only a small number of proved cases of avian infection have been reported in humans Morphologic and cultural differences between the three types are somewhat variable and animal inoculation is resorted to for positive identification The human type causes disease in the guinea pig but not in the rabbit the bovine type in both the guinea pig and the rabbit and the avian type in birds and rabbits but not in the guinea pig

The tubercle bacillus is about 1 0 to 4 0 μ in length and 0 3 μ in thickness Beaded and granular forms have been observed with both modified Gram and acid fast stains but recent evidence indicates that many of these are artefacts of the staining process True granular forms do occur particularly in older cultures and are identified by their red rather than purple color lack of distention of the cell wall and failure to disappear with the addition of alcohol Evidence for a filtrable virus or zoogleic stage in the life cycle of the tubercle bacillus is not entirely convincing for the present it must be assumed that reproduction occurs by fission The distinguishing tinctorial property of the tubercle bacillus—namely its ability to resist decolorization by acid alcohol when stained with basic fuchsin—is known to be related to the waxy component and probably specifically to mycolic acid Curiously the structural integrity of the cell is also involved for grinding the bacilli between glass slides destroys acid fastness whereas prolonged extraction with fat solvents does not alter this property

Avirulent dissociates of virulent strains of tubercle bacilli may be produced by appropriate cultural techniques and occasionally tubercle bacilli of unusually low virulence for laboratory animals have been isolated from man It has not been definitely established however that true dissociation can occur in the human body A simple morphologic differentiation between virulent and avirulent dissociates has been described by Middlebrook and Dubos—namely that virulent cultures grow in long tightly formed cords with individual bacilli parallel to each other whereas avirulent organisms are haphazardly arranged The correlation between cording and virulence is not absolute however

Chemically the tubercle bacillus is unique in its high lipid content which makes up one fourth to one third of its dry weight The lipids are composed of phosphatides acetone soluble fats and waxes These substances probably account for the unusual resistance of the tubercle bacillus to bactericidal agents to drying and to wide temperature variations They are not however as was once thought situated on the surface of the cell as a thick capsule but are distributed throughout the body of the bacillus

Tubercle bacilli are strict aerobes and are usually isolated on solid media containing potato egg yolk and glycerin Growth is slow 4 to 6 weeks being required for colonies to develop Because of their high lipid content tubercle bacilli are hydrophobic and grow in clumps on the surface of ordinary liquid media Dubos has developed a liquid medium containing a complex ester of oleic acid Tween 80 which coats the bacilli making them hydrophilic and provides rapid diffuse submerged growth This medium has become a standard tool for quantitative laboratory studies

TRANSMISSION

Inhalation of air containing tubercle bacilli is the most important means of acquiring tuberculous infection in man The bacilli may be transmitted in droplets of saliva or sputum Transmission may occur also from inhalation of particles of dust laden with viable organisms a method which is possible because of the peculiar resistance of the tubercle bacillus to desiccation and exposure Tubercle bacilli are killed within a few hours in direct sunlight but survive up to 5 days in a well lighted room up to 5 months in the dark and as long as a year and a half in the refrigerator

In addition to inhalation tubercle bacilli may enter the mouth and pharynx by direct or indirect

gins Seeding is common in the upper parts of the lungs producing lesions which appear in x rays as small indistinct areas of increased density These foci tend to heal with fibrosis and calcification Focal hematogenous lesions in other organs may regress and heal or they may lie dormant for many years and eventually cause progressive destructive lesions

Reinfection Tuberculosis Tuberculosis in the adult is regarded as usually being reinfectious in character i e infection in individuals whose immunologic state and tissue response have been altered by previous contact with the tubercle bacillus The basic manifestations of this altered response are as indicated in the section on Immunity an intense local inflammatory reaction suppression of proliferation of the bacilli and inhibition of their spread These features are observed in cases of reinfection tuberculosis in human beings just as they are in experimental animals in the Koch phenomenon in fact adult reinfection pulmonary tuberculosis (phthisis) is in essence as pointed out by Pinner a Koch phenomenon in the lung There is an intense local reaction of the tissues with a tendency to chronicity marked fibrosis excavation and restriction in the involvement of lymph nodes

Reinfection tuberculosis in the adult usually begins as a small caseopneumonic focus in the posterior portion of the upper lobe less commonly it may be present in the apical portion of a lower lobe While the patient is still asymptomatic this lesion can often be seen as a small area of density with indistinct borders in the infraclavicular region between the first and third anterior ribs This focus is commonly referred to as an *early infiltrate*

One of the unsolved problems of tuberculosis is the source of the tubercle bacilli which are responsible for the early infiltrate There are two possibilities One is inhalation of bacilli from without giving rise to an entirely new infection in the upper portion of the lung—i e the establishment of a true exogenous reinfection The other possibility is local exacerbation or transmission to the local site of bacilli which have lain dormant somewhere in the body following subsidence of the primary infection this is known as endogenous exacerbation The relative frequency with which exogenous reinfection and endogenous exacerbation are responsible for the early infiltrate is not known both undoubtedly occur

Adult tuberculosis as discussed in the preceding paragraphs is assumed to be largely reinfectious in nature It should be stated again however that an increasing number of cases of adult tuberculosis are instances of primary infection and unequivocally exogenous in origin

Pulmonary tuberculosis in the adult usually but not invariably begins as an early infiltrate In an occasional instance tuberculous pneumonia may follow the rupture of a caseous hilar lymph nod this is seen with increasing frequency in older individual Clinically suggestive evidence also indicates that pneumonic lesions may develop when a large inoculum of bacilli is carried suddenly to a portion of the lung from some endogenous focus Contiguous spread from nodular foci at the extreme pulmonary apex a mode of development thought at one time to account for virtually all phthisis unquestionably occurs in some cases Finally hematogenous seeding may give rise to bilateral foci usually in the upper parts of the lungs which remain interstitial and cause relatively few symptoms or ulcerate through the bronchi and gradually produce bronchogenic phthisis

Once formed the early infiltrate may regress and heal completely This may occur in ambulatory asymptomatic individuals but the value of bed rest in aiding this process is well established All too often the early infiltrate progresses to the characteristic chronic destructive form of pulmonary tuberculosis Caseation is followed by liquefaction and cavitation Intrabronchial aspiration gives rise to new parenchymal foci where the process is repeated The presence of bacilliferous sputum also leads in a large percentage of cases to lesions of the bronchial and tracheal mucosa Reparative processes supervene with resorption and fibrosis but the nature of the lesions especially the cavities which continually discharge infective material into the bronchial passages tends to foster chronicity and gradual extension of the disease

As pulmonary tuberculosis progresses increasingly large numbers of tubercle bacilli are expelled in the bronchopulmonary secretions and are responsible for lesions in the larynx the mouth and the intestinal tract The pathogenesis of other forms of extrapulmonary tuberculosis may be stated briefly Tuberculosis of the kidneys epididymis prostate fallopian tubes adrenals bones brain eyes lymph nodes and other organs not in direct contact with the external environment is lymphohematogenous in origin Seeding of these organs may occur during the active primary stage of infection causing progressive destructive lesions at that time or after many years of latency Hematogenous dissemination may also occur during reinfection tuberculosis in adults The internal organs vary considerably in their susceptibility to tuberculous infection Some such as those listed above are relatively frequently involved while others including the pancreas thyroid ovary spleen heart liver and skeletal muscles are rarely the site of progressive lesions

reaction which develops much more rapidly than with the primary infection (2) suppression of multiplication of the organism and (3) inhibition of spread of the bacilli with little or no involvement of the regional lymph nodes and a greatly decreased tendency toward hematogenous dissemination

Tuberculin hypersensitivity appears at approximately the same time as acquired resistance from 2 to 6 weeks following the initial infection The two are closely associated although the degree of hypersensitivity is not a measure of immunity In man a definite but limited degree of acquired resistance occurs as a result of a primary infection

Mechanisms of Resistance The basic mechanisms underlying native and acquired resistance to the tubercle bacillus are unknown Native resistance seems to be determined by conditions existing within the mononuclear phagocytes in which large numbers of tubercle bacilli become segregated soon after entering the body In the susceptible body bacilli multiply freely in the monocytes while in the natively resistant body the environment is for some unknown reason unfavorable causing the organisms to be inhibited and gradually to die

In acquired resistance humoral immunity has not been found to play the important role it does in most other infections Humoral antibodies have been demonstrated repeatedly in animals and patients infected with the tubercle bacillus but they appear irregularly do not increase the resistance of normal animals to tuberculosis and have not been found in vitro to render tubercle bacilli more easily phagocytable by opsonization

Lurie has observed an increased metabolic activity of phagocytes in natively resistant or immunized rabbits and studies indicate that hormones may play an important role in immunity Genetically susceptible rabbits have been found to secrete about twice as much hydrocortisone as animals which are genetically resistant These observations may lead to a better understanding of immunity in tuberculosis

PATHOGENESIS

Primary Tuberculosis Most tissues exposed to direct contact with bacilli are protected by local mechanical defenses under ordinary circumstances but may become infected when these defenses are broken Thus the primary focus is observed occasionally on the fingers on ear lobes that have been pierced on the tonsils and on the conjunctiva

In the lung the primary focus is usually near the pleura and occurs most frequently in the upper part of the lower lobe or the lower part of the upper lobe Initially exudative in character the primary focus rapidly undergoes caseation Tubercle bacilli escape freely and are carried to the bronchopulmonary and tracheobronchial lymph nodes which become greatly enlarged and undergo exudation and caseation The combination of the primary focus and the enlarged regional lymph nodes is commonly referred to as the *primary complex*

It has become increasingly common for individuals to attain adult life without contracting a primary tuberculous infection It is a curious fact however that in white adults it is unusual to observe the x ray enlargement of the tracheobronchial lymph nodes so characteristic of primary infections in childhood Both from the standpoint of x ray appearance and clinical course lesions in recently tuberculin negative adults are indistinguishable from those clearly due to reinfection tuberculosis Exceptions have been observed but are uncommon In Negroes typical primary complexes are observed in adults as well as in children This racial difference suggests that an age determined native resistance may modify the characteristics of primary infections in white adults while in Negroes who have a lower degree of native resistance the age determined difference is lacking

Deviations from the classic primary complex have been described by Terplan The parenchymal focus and the lymph node component have been observed to occur separately and new typical primary complexes have been noted in lungs in which the true initial complexes are in a relatively advanced state of healing

In the great majority of instances the primary complex undergoes gradual healing with encapsulation of the parenchymal and lymph node components and eventual calcification By x ray the lesions gradually recede from the periphery and eventually leave small areas of calcific density usually less than 1 cm in diameter Bacteriologically in over 80 per cent of adults who have arrested a primary infection in childhood the calcified primary complex is sterile In these instances the possibilities of endogenous exacerbation are not completely excluded however for tubercle bacilli may remain viable in lesions of the paratracheal or upper mediastinal nodes

In a small percentage of cases there is progression of the primary complex this accounts for most of the fatalities in infants and children Progression occurs in the following ways (1) direct extension or intrabronchial spread (2) massive lymph node caseation with rupture into a bronchus resulting in tuberculous pneumonia and (3) hematogenous dissemination Hematogenous dissemination occurs frequently during the course of primary tuberculosis and may result in the full blown picture of miliary tuberculosis with death in a few weeks or may merely give rise to seeding in various or

Occasionally a gross hemoptysis may usher in the disease the patient being unaware of any previous symptoms Bleeding results usually from the ulceration of vessels in tuberculous cavities and the natural tendency of the infectious process to cause vascular thrombosis is an important factor in preventing massive hemorrhages in the majority of patients with cavitary disease Large hemoptyses usually occur without warning and frequently begin when the patient is asleep Ordinarily not more than 300 ml of blood is produced Dark clots of blood are usually brought up for several days if the cough mechanism is inadequate there may be blockage of a main bronchus with collapse of one or more lobes Bleeding may recur at frequent intervals and transfusions may be needed In an occasional instance the hemorrhage is massive and fatal this usually occurs with old fibrotic disease and the patient drowns within a few minutes One of the greatest hazards of hemoptysis is the danger of spreading the infection throughout the lungs Depending on the number of tubercle bacilli present in the bloody fluid posthemoptysic spreads vary in extent from scattered finely mottled infiltrations to massive tuberculous pneumonia

As pulmonary tuberculosis progresses and especially with cavitary disease ulcerations or granulomatous infiltrations frequently appear in portions of the tracheobronchial tree draining affected lung tissue with *wheezing* as a common symptom Endobronchial disease may alter the treatment and therefore this symptom should be carefully sought for Wheezing may also occur in the absence of demonstrable ulcerations or granulations and is then presumably caused by mucosal swelling or retained secretions It should be noted that tuberculous tracheobronchitis occasionally occurs in the absence of demonstrable parenchymal disease

Tuberculous Pneumonia The clinical onset of tuberculosis occasionally may be an acute pneumonic episode especially in Negroes in children and in elderly individuals both white and colored The sudden aspiration of a dose of bacilli sufficiently large to cause a pneumonic lesion results usually from the abrupt emptying of a cavity from a hemoptysis or from the rupture of a caseous node into a bronchus Fever chilly sensations cough and chest pain are noted and the condition can easily be confused with primary atypical pneumonia The temperature is usually not above 102 F though it may rise to 104 or 105 F and the white blood count is in most instances not elevated above 15 000 Untreated tuberculous pneumonia may run a malignant course with death in from 1 to 3 months or the process may gradually subside and become chronic

Pleurisy with Effusion This condition is common among young adults and its pathogenesis and significance need emphasis The pleura usually becomes involved as a result of direct or lymphatic extension from an underlying parenchymal process and the lesion in the lung often is not of sufficient size to be visible on the x ray Whether the pleura can also be infected directly by way of the blood stream is a matter of dispute Animal experiments indicate that parenteral injections of tubercle bacilli rarely result in direct infection of serous cavities The not infrequent occurrence of bilateral effusions on the other hand is often cited as evidence that infection of the pleural surfaces may result from direct hematogenous seeding Chest pain and fever are the initial symptoms the pain may be sharp and pleuritic in character or it may begin as a dull ache or uncomfortable sensation in the lower chest In the more acute cases there is marked prostration with a high fever and a stormy course for 2 or 3 weeks More commonly the temperature is only moderately elevated and the patient does not feel particularly ill except for the pain in the chest Clear yellow fluid is obtained by aspiration and tubercle bacilli are recovered by culture or guinea pig inoculation in approximately 50 per cent of the cases Whether the organism is recovered or not experience has shown that without treatment 30 to 50 per cent of the patients develop clinical and x ray signs of active pulmonary tuberculosis within 5 years These figures are sufficiently high to warrant the assumption that all cases of "nonspecific" pleurisy with effusion are caused by tuberculosis and they should be treated accordingly Details of management will be outlined in a subsequent section

Physical and X ray Examination

The widespread use of the x ray during the past 25 years has demonstrated the marked limitations of physical examination in detecting and appraising the lesions of pulmonary tuberculosis As a result the tendency at present in many quarters is virtually to ignore the physical examination altogether this is lamentable for the physical signs contribute information which when correlated with the x ray findings gives a more complete understanding of the nature and activity of the parenchymal disease

Early asymptomatic infiltrations are usually missed on routine physical examination and indeed it is often surprising how extensive the x ray infiltrations may become before definite physical abnormalities are detected Crepitant posttussic rales may be noted over a small area in minimal lesions although rales are not of themselves conclusive evidence of activity With larger lesions especially after cavitation develops dullness and moderately coarse rales are usually elicited With pneumonic lesions the classic signs of consolidation are noted

PULMONARY TUBERCULOSIS

Manifestations

The onset of symptoms of pulmonary tuberculosis is in many instances *insidious* In the early stages and at times when moderate progression has occurred the patient is usually *entirely asymptomatic* and may remain so for a considerable period This cannot be emphasized too strongly more and more early asymptomatic cases are being discovered as a result of routine films and x ray surveys

The earliest symptoms are constitutional and probably result chiefly from the absorption of tuberculoprotein into the circulation of the hypersensitive body *Fever* is one of the commonest manifestations of tuberculosis and usually begins as a slight elevation of the temperature in the late afternoon or evening This elevation may occur daily gradually attaining higher levels over a period of weeks or months or it may subside altogether and reappear intermittently as the patient passes through a series of grippelike episodes It is characteristic for fever to be relatively well tolerated in patients with tuberculosis even with a temperature elevation to 102 or 103 F Except for sensations of warmth and flushing the patient is often quite comfortable and in some instances is even euphoric

Fatigue and malaise are among the earliest symptoms noticed by the patient They usually first manifest themselves as excessive tiredness at the end of the day and may lead the patient to restrict his activities in the evening in order to get more rest In other instances particularly when the subject refuses to modify his routine he may become irritable and morose Eventually in far advanced disease profound asthenia is often present

Weight loss is usually noted somewhat later than the above symptoms and may not be present for many months unless the disease runs a malignant course Anorexia and indigestion are associated symptoms and seem to vary with the severity of the other manifestations Anorexia may provide a clue from the standpoint of differential diagnosis tuberculosis at this stage can be confused with diabetes and thyrotoxicosis and in both these conditions loss of weight is characteristically associated with an increase in appetite

Chilly sensations may be noted as the toxemia progresses particularly when the temperature rises abruptly in the evening *Night sweats* are considered classic manifestations of tuberculosis but actually do not occur in most instances until the disease is fairly far advanced *Tachycardia* occurs along with the fever *Headache* is noted in some individuals in the evening when the temperature is elevated but the symptom usually subsides by morning and is absent during the daytime

Menstruation is said to be disturbed in tuberculosis but this statement is based upon the situation occurring in far advanced disease In the early stages the menses are usually normal and become irregular and scanty only as the disease progresses Amenorrhea may occur in the later stages particularly when the condition becomes terminal For reasons not entirely clear hemoptysis seems to occur more frequently during the menstrual period

Since examination of the lungs in the early stages is negative in most instances and the blood count and sedimentation rate may be entirely normal the importance of the chest x ray in diagnosis cannot be overemphasized

In many patients with pulmonary tuberculosis the onset of symptoms is *relatively sudden* A characteristic story is that of a bad cold or "influenza without awareness of any prior disability The cold—especially the cough—persists while the constitutional manifestations may subside temporarily giving the patient the feeling that he is recovering Some individuals may recall a slight morning cough of some months duration attributed usually to irritation from smoking Cough is characteristically first noted in the morning because secretions formed in the lungs during the night flow into the bronchi and trachea and stimulate the cough reflex on arising Once these passages are cleared the patient coughs infrequently or not at all until the next morning when another mild paroxysm occurs As the disease progresses the secretions are formed in larger amounts and the cough becomes more troublesome occurring throughout the day and night

Along with cough there is expectoration of *sputum* In early cases a few flecks of pus may be seen in the mucus and later the sputum becomes predominantly purulent in character As cavitation progresses liquefied caseous material is formed in increasing amounts until 2 or 3 oz of sputum are produced daily In caseous pneumonic lesions with cavitation and liquefaction the purulent matter is usually green or greenish yellow Later as the clinical condition improves the sputum is yellowish and more mucoid Tuberculous sputum is not foul except in rare instances in which the pulmonary lesions become secondarily infected with anaerobes Layering does not usually occur a feature which is at times helpful in differentiating tuberculosis from lung abscesses Late in the course of the disease secondary infection of tuberculous cavities does occasionally occur and the patient may become exhausted by his efforts to bring up 300 or 400 ml of sputum daily

Hemoptysis is commonly associated with cough and expectoration and ordinarily consists of streaking of the sputum with small amounts of blood

to 1 0 mg OT Recent evidence indicates that the *second strength sometimes gives false positive re* actions and the present trend is towards using a single intermediate strength concentration of P P D namely 0 001 mg

The tuberculin patch test is often used in chil dren to avoid the use of needles It is less reliable however and if negative should be followed by the intracutaneous test if an accurate appraisal of the skin reactivity is desired

Laboratory Findings

Recovery of Tubercle Bacillus Aside from the x ray the most important laboratory procedures used in the diagnosis and management of patients with tuberculosis are those concerned with the isolation of tubercle bacilli from sputum gastric wash ings urine feces spinal fluid serous and purulent effusions abscesses and draining sinuses

Sputum may be absent or present in only small amounts early in the morning in patients with mini mal tuberculosis and a few flecks of mucopurulent material obtained at this time may be adequate to make the diagnosis The material is usually exam ined first by the direct smear The Ziehl Neelsen method of staining is the most widely used al though a fluorescent dye carbolauramine has be come popular in recent years Fairly large numbers of tubercle bacilli must be present to be seen on the direct smear Therefore if this is negative 20 ml or more of sputum is collected digested with acid or alkali concentrated by centrifugation neu tralized and the sediment smeared stained and examined With this technique a significantly higher percentage of specimens is positive than on direct smear If negative on smear the concentrated sedi ment is cultured or inoculated into guinea pigs or both Twenty to thirty per cent more positives are obtained by culture or guinea pig inoculation than by smear of the concentrated sediment The rela tive merits of cultures and guinea pig inoculations are debated but the results with cultures are so favorable that in many laboratories the more la borious and expensive guinea pig method has been abandoned

If no sputum is produced the *gastric contents* should be aspirated shortly after the patient awak ens in the morning Smears of the gastric contents may give false positive results therefore the ma terial is digested concentrated and cultured or inoculated into guinea pigs In minimal cases of pulmonary tuberculosis prior to the development of cavitation discharges carried into the bronchial tree and swallowed by the patient are small in amount and many cultures of the gastric contents may be necessary to recover tubercle bacilli For example in one study it was found that 68 per cent of minimal cases had at least 3 negative speci mens before a positive was obtained and in another series of 61 patients from 5 to 14 negatives were reported prior to the first positive culture Once cavitation develops the discharges increase in amount and bacilli can be recovered by cultures of the sputum or gastric contents with comparative ease A series of negative sputum or gastric cul tures in the presence of cavitation provides strong presumptive evidence against the diagnosis of active pulmonary tuberculosis

The basic principles outlined for sputum and gastric contents apply to the recovery of tubercle bacilli from other sources Minor modifications are necessary especially in preparing and concentrat ing urine and stool specimens With spinal fluid tubercle bacilli are often detected by smear or cul ture of the pellicle which forms if the specimen is left in the icebox overnight

Sedimentation Rate The sedimentation rate is normal in the majority of individuals with minimal tuberculosis In more advanced febrile cases the sedimentation rate usually is elevated and often is used as an index of the progression or regression of the disease This use has definite limitations how ever since the rate may be normal in patients on absolute bed rest in spite of progressive intrabron chial disseminations and conversely a sudden in crease in the rate may accompany the onset of a relatively insignificant complication such as mild pleurisy

Blood Hematologic changes in tuberculosis are relatively slight In minimal cases the blood count is usually normal but as the disease progresses there may develop a mild normochromic normo cytic anemia Even in far advanced cases the anemia usually is not marked except in the pres ence of extrapulmonary complications such as in testinal tuberculosis or amyloidosis A mild leuko cytosis may be present in progressive febrile stages with a count of 10 000 to 15 000 but even in acute tuberculous pneumonia the total white count is rarely above 15 000 An increase in monocytes with a decrease in lymphocytes is regarded by some ob servers as indicative of progression of the disease and in experimental animals this appears to be well substantiated In man however the lymphocyte monocyte ratio and other prognostic guides such as the Medlar index are of limited value Exceptions to some of the above statements should be noted in widespread acute tuberculous pneumonia for ex ample the total white count may occasionally be well above 20 000 with a polymorphonuclear count of over 95 per cent Similarly in acute miliary tu berculosis there may occur a high grade leukocy tosis and at times even a leukemoid blood picture or there may be a marked leukopenia

Urine Changes in the urine in pulmonary tu berculosis as in other chronic febrile diseases con

and as cavitation develops coarse bubbling rales appear especially at the base of the cavities where liquefied pus tends to accumulate Even with large cavities demonstrable on the x ray however the classic signs of tympany and amphoric breathing are often absent because the soft shaggy cavity walls and surrounding structures do not act as good resonators In old fibrocaseous lesions the walls are relatively thick and rigid and the classic signs of cavitation may be present Tension cavities associated with bronchial disease preventing normal egress of air during expiration also produce atypical signs With long standing disease extensive fibrosis causes contraction and distortion of the pulmonary tissue In such instances a wide variety of physical signs such as bronchial breath sounds coarse rales deviation of the trachea spasm and atrophy of various chest and neck muscles and diminished movements of one hemithorax are noted

From an x ray standpoint the early infiltrate is usually observed in the infraclavicular region although it may be located entirely above the clavicle or in the midlung field As the infiltrations progress and enlarge the x ray appearance of pulmonary tuberculosis may be indistinguishable from various nontuberculous conditions Tuberculous cavities especially when located in the lower lung fields closely simulate nontuberculous lung abscesses Similarly the tuberculous nature of bronchopneumonic or lobar consolidations cannot be determined on the basis of the x ray alone The limitations of a single film in determining whether an infiltration is tuberculous and of assessing its activity leads to serious diagnostic and therapeutic errors

Aside from its diagnostic limitations the x ray film may at times give misleading impressions concerning the functional status of the lungs For example in patients who have had pleural effusions or extensive nodular bronchogenic disseminations following hemoptysis the lung fields may eventually become almost entirely clear by x ray although pulmonary function remains markedly impaired Careful physical examination will reveal the presence of impaired function in such cases and will lead to more precise pulmonary function studies if surgery is contemplated

Tuberculin Test

Tissue hypersensitivity to tuberculoprotein results from the production of tuberculous tissue in the body by intact whole tubercle bacilli either living attenuated or dead A positive tuberculin test indicates therefore that an individual has or has had such a focus of tuberculous tissue in his body It does not indicate that he harbors a clinically significant lesion or that any of his present signs or symptoms are necessarily due to tuberculosis active or inactive The chief value of the test lies in exclusion If negative it can be fairly reliably concluded that the patient does not have active tuberculosis virtually all individuals with active tuberculosis have a positive tuberculin reaction Exceptions are sometimes noted during the course of intercurrent infections especially measles and influenza late in the course of pregnancy and in some terminal cases of tuberculosis The tuberculin skin reaction may turn negative after a period of years in individuals who have arrested and healed a primary tuberculous infection the frequency with which this occurs is not known but many well documented instances are on record The increasing incidence of negative tuberculin reactions in young adults has enhanced the diagnostic value of the test in recent years Only 20 to 30 per cent of young men in the Armed Forces during World War II were tuberculin positive in this age group the skin reaction is particularly helpful in ruling out tuberculosis in the presence of obscure fevers and undiagnosed pulmonary conditions

The most reliable and accurate method of performing the tuberculin test is the intracutaneous or Mantoux test in which 0 1 ml of suitably diluted tuberculin is injected intradermally into the skin of the forearm If positive induration (5 mm or more) appears at the local site in 24 to 72 hr and is surrounded by an area of inflammation varying from one to several centimeters Intense local reactions occur if the dose of tuberculoprotein is too large causing tissue necrosis and lymphangitis extending to the regional nodes Absorption of tuberculoprotein into the circulation of the highly hypersensitive body causes constitutional symptoms chiefly malaise and fever and may produce focal reactions around tuberculous lesions throughout the body To avoid these untoward reactions small doses of tuberculin should be used for the initial test with gradually increasing amounts thereafter at intervals of 3 or 4 days until the test becomes positive If old tuberculin (OT) is used the initial dose is usually 0 01 mg (0 1 ml of a 1 10 000 dilution) in individuals suspected of being unusually hypersensitive the initial dose may be reduced to *0 001 mg If the reaction is negative tenfold incre*ments in the amount of OT are employed for subsequent tests An individual is ordinarily considered tuberculin negative if he fails to react to 1 0 mg although some observers prefer to increase the amount to 10 mg In recent years the purified protein derivative (P P D) of Seibert has partially replaced OT because it gives more uniform results and minimizes false positive reactions It is available commercially in two strengths the first (0 00002 mg) being roughly equivalent to 0 01 mg OT and *the second (0 005 mg) corresponding*

exposure the coccidioidin skin test smears and cultures of the sputum for *Coccidioides immitis* and precipitin and complement fixation tests of the patient s serum are the procedures used in con firming or excluding the diagnosis *Histoplasmosis* recently has been suspected of causing pulmonary calcifications similar to those occurring in tubercu losis because of the observation that many indi viduals in the South Central states with pulmonary calcifications have positive histoplasmin skin tests and negative tuberculin reactions Other mycotic infections such as *actinomycosis* and *blastomycosis* may at times simulate tuberculosis but the fungi involved usually can be readily recovered from the sputum

Sarcoidosis Typically the patient with sarcoido sis is afebrile and has a negative tuberculin test and biopsy of lymph nodes reveals tubercles without caseation Fever may be present however and in about 20 per cent of cases the tuberculin test is positive Pulmonary infiltrations vary from hilar adenopathy to extensive parenchymal involvement which can resemble tuberculosis very closely In some cases differentiation is extremely difficult and the situation is further complicated by the fact that some patients with a diagnosis of sarcoidosis eventu ally die of tuberculosis

Carcinoma of Lung Carcinoma of the lung with chronic cough blood streaked sputum fever and weight loss may present a clinical picture very simi lar to tuberculosis in older individuals Carcinomas located peripherally produce fewer symptoms but may present an x ray appearance indistinguishable from that of tuberculosis Patients with lesions sus pected of being carcinomatous from whom tubercle bacilli cannot be recovered should be subjected to early thoracotomy It should be noted that both tuberculosis and carcinoma are occasionally present in the same patient

Cardiovascular Disorders These may produce symptoms suggestive of tuberculosis Hemoptysis occurs frequently with mitral stenosis and is occa sionally observed with hypertension Long standing pulmonary congestion such as occurs in patients with mitral stenosis causes pulmonary fibrosis in fected pulmonary infarcts may develop into ab-scesses suggestive of tuberculous cavitation

Other Conditions Mediastinal cysts bacterial pneumonia lipoid granuloma lymphomas ame biasis aortic aneurysms and metastatic neoplasms may be confused with tuberculosis Careful evalua tion and study including the exclusion of tubercu losis by the failure to find tubercle bacilli usually will lead to the correct diagnosis

Evaluation of Need for Treatment

In patients with progressive symptomatic pul monary tuberculosis the clinical and x ray findings are usually characteristic and the diagnosis and need for treatment are established readily In some situations however the diagnosis and degree of activity and therefore the need for treatment are more difficult to ascertain At the outset it may be stated that old calcified primary complexes nodu lar fibrotic areas at the extreme apices and ad hesions and scarring due to old pleurisy are not indications for treatment Individuals with these lesions should have yearly x ray examinations since dormant foci can give rise to active disease during periods of lowered resistance

Minimal infraclavicular infiltrations often de tected as a result of x ray surveys require careful evaluation which in most instances should be carried out with the patient at bed rest This is particularly true of individuals under twenty five years of age Hazy poorly circumscribed shadows indicate exudative unstable lesions while dense sharply circumscribed infiltrations usually represent old arrested disease which is unlikely to progress Serial x rays are the best means of following a lesion and determining its activity These should be made at least once a month and sometimes more frequently in young adults with exudative lesions Gastric washings should be cultured re peatedly Careful clinical observations and serial roentgenograms over a period of at least 6 months are usually adequate to determine the activity of the lesion Chemotherapy may be instituted at the outset if clinical and x ray findings indicate that the lesion is almost certainly active

Treatment

The advent of effective chemotherapeutic agents has brought about great changes in the treatment of tuberculosis during the past decade It is now generally agreed that all patients with active tu berculosis should receive prolonged chemotherapy and that bed rest is necessary for only part of the period of treatment Collapse therapy is being used less and less so that initial treatment for most patients consists of rest and the administration of antimicrobial drugs If after several months the sputum remains positive or if there are open cavi ties or large residual necrotic foci surgical excision of the involved areas is performed The basic prin ciples of therapy can thus be stated very simply but a great deal remains to be learned about the optimal indications for and details of bed rest chemotherapy and surgical management of the disease

Ten years ago it was agreed that *bed rest* was the most important single measure available for the therapy of tuberculosis The course of the dis ease is so changed by chemotherapy however that modifications of the formerly strict regimens are now employed Fever and toxicity are definite indi

sist chiefly of intermittent traces of albumin without other significant abnormalities Renal tuberculosis is not uncommon and frequent urine examinations should be made noting especially persistent proteinuria and an abnormal number of erythrocytes and leukocytes If these are present *pyelograms* are indicated and concentrated urine specimens should be cultured and inoculated into guinea pigs Except in rare cases an active renal lesion is present if tubercle bacilli are recovered repeatedly from the urine and drug therapy is indicated

Other Tests A number of serologic tests have been employed in tuberculosis but none has been found to be of practical diagnostic or prognostic value The complement fixation reaction for example is positive in less than 50 per cent of patients with minimal lesions and false positive reactions are obtained in over 10 per cent of individuals with no evidence of active tuberculosis

Differential Diagnosis

The onset and course of pulmonary tuberculosis *vary widely and may simulate a great number of* other diseases The outstanding conditions which may be confused with tuberculosis and the main differential features will be considered briefly

Psychoneurosis Patients with purely functional disorders frequently present complaints similar to those of early pulmonary tuberculosis Malaise easy fatigability and inability to concentrate are common symptoms and there may be anorexia with slight weight loss A chronic hacking cough may be present due to irritation of the respiratory passages from smoking A careful evaluation of these complaints will usually give a clue to the correct diagnosis A chest x ray is an essential part of the examination of patients with the symptoms described above

Endocrine Disorders Two endocrine disorders *hyperthyroidism* and *diabetes* are commonly manifested by weight loss and easy fatigability In contrast to tuberculosis however the weight loss is associated with an increased appetite rather than with anorexia Negative chest x rays in addition to glycosuria and an abnormal glucose tolerance test in diabetes and an elevation of the basal metabolic rate in hyperthyroidism lead to the correct diagnosis

Obscure Fevers Tuberculosis is always to be considered in the differential diagnosis of fevers of unknown origin With a negative chest x ray the fever may be caused by early miliary tuberculosis or by an extrapulmonary tuberculous focus and localizing signs should be sought for (see p 73)

Pulmonary Fibrosis and Emphysema Pulmonary fibrosis and emphysema with cough weakness dyspnea and at times streaking of the sputum are relatively common in older individuals Tuberculosis is in some cases the cause or is an associated condition and therefore the sputum should be examined carefully for tubercle bacilli Pneumoconioses especially silicosis should be kept in mind and the patient questioned concerning possible industrial exposure *Nodulation* more dense near the hilar regions and extending peripherally through both lung fields is the characteristic x ray appearance of silicosis With the development of a superimposed tuberculous infection larger confluent shadows appear and the constitutional manifestations of tuberculosis are usually present although it may be very difficult to recover tubercle bacilli from the sputum

Nontuberculous Lung Abscess This affection which may be roentgenologically indistinguishable from tuberculosis usually has an acute onset with chills fever and leukocytosis The sputum may or may not be foul depending on the organisms involved The differential diagnosis is usually relatively simple since acid fast bacilli are almost always readily demonstrable in patients with tuberculous cavities Clubbing of the fingers may develop in 4 to 8 weeks in the presence of a nontuberculous abscess Nontuberculous abscesses may become chronic and when seen at this stage especially in conjunction with hemoptysis may be very suggestive of tuberculosis Sputum studies plus a careful review of the original signs and symptoms usually will clarify the situation (see p 1394)

Bronchiectasis Bronchiectasis is usually associated with a chronic productive cough and is one of the commonest causes of hemoptysis Clubbing of the fingers is common while in tuberculosis it is rare Bronchiectasis usually involves the lower portions of one or both lungs but is sometimes situated at the apex The x ray may be completely negative or there may be increased linear densities extending outward and downward from the hilar regions Moderately coarse rales usually are noted over the involved areas The failure to find acid fast bacilli in the sputum and the demonstration of radiographic abnormality by bronchogram confirm the diagnosis Not infrequently tuberculosis and bronchiectasis are found to coexist

Primary Atypical Pneumonia This presents a clinical and x ray picture which may be indistinguishable from pulmonary tuberculosis The absence of cavitation the failure to find tubercle bacilli in repeated examinations of the sputum and the eventual complete clearing of the parenchymal lesions are the important differential features

Mycotic Diseases *Coccidioidomycosis* presents a clinical and x ray picture similar to pulmonary tuberculosis This condition is of national importance because of the large number of individuals who were in the endemic areas of the Southwest during the *Second World War A history of possible*

ability to produce tuberculin hypersensitivity With metabolically inactive organisms such as occur in poorly oxygenated lesions or after previous therapy isoniazid is taken up reversibly and does not interfere with acid fastness nor sensitizing ability These observations undoubtedly explain in part why tubercle bacilli are not often eradicated from tuberculous lesions in patients During therapy drug resistant organisms emerge quite rapidly and it is customary therefore to administer another antimicrobial agent simultaneously With isoniazid however the appearance of resistant mutants is not so clearly related to a failure to show continued improvement as it is with streptomycin This may be related to Middlebrook s observation that some isoniazid resistant tubercle bacilli do not form catalase and have little or no virulence when injected into guinea pigs Failure of these organisms to grow in tissues may be due to susceptibility to the toxic effects of hydrogen peroxide Catalase positive isoniazid resistant mutants which are fully virulent also occur and probably account for progression of the disease which is observed after isoniazid resistance has developed

Isoniazid is usually given orally in a total daily dose of 3 to 10 mg per kg body weight For adults the arbitrary selection of a daily dose of 200 to 300 mg given in divided doses at 8 or 12 hr intervals is satisfactory It has been shown however that some patients acetylate the drug at an unusually rapid rate and require 600 to 1 000 mg daily to provide adequate tissue concentrations These higher doses are used routinely in a few clinics When high doses are employed 50 to 100 mg pyridoxine should also be given daily to prevent peripheral neuritis (see p 826)

Drug Regimens It is generally agreed that with few exceptions two and sometimes three drugs should be administered simultaneously in the treatment of all forms of tuberculosis The exceptions apply to isoniazid which is probably adequate when used alone for the treatment of minimal pulmonary tuberculosis and tuberculous pleurisy with effusion Isoniazid is also used alone in some clinics for a year or two following an initial 3-month period of multiple drug therapy

Of the regimens available it has been definitely shown that those containing isoniazid produce superior results Thus the combination of streptomycin and PAS which was so widely used for a few years is now employed for initial therapy only under unusual circumstances Isoniazid PAS is probably most widely used for the initial treatment of pulmonary tuberculosis at the present time The results are comparable or nearly so to those obtained with any other combination and both drugs are taken by mouth Another important advantage is that streptomycin is held in reserve for use later in conjunction with surgery if it is needed With this combination the effective blood levels of both drugs are higher than when either is given alone possibly because isoniazid and PAS compete for the same acetylation mechanism

Results with isoniazid streptomycin are perhaps slightly superior in far advanced cases to those obtained with isoniazid PAS particularly when streptomycin is injected daily rather than twice a week The chief disadvantage namely that the two most potent drugs are likely to become ineffective because of the development of resistant organisms is not of great importance since the relapse rate is only about 5 per cent Furthermore the combination of viomycin PAS is available if needed for surgical coverage In older individuals who are more susceptible to the toxic effects of streptomycin some experts prefer to avoid this drug and to select isoniazid PAS instead it is apparent from what has been said that both isoniazid PAS and isoniazid streptomycin have their advantages and it is desirable to select the combination most suitable for each individual patient The use of three drugs simultaneously (isoniazid streptomycin and PAS) has not been found superior for the treatment of pulmonary tuberculosis For certain extrapulmonary forms of the disease to be considered later triple-drug regimens are commonly used

Duration of Chemotherapy The optimal duration of therapy cannot be stated at present The most important trend to be noted is a gradual lengthening from 2 to 3 months in the years prior to 1949 to regimens which call for 1 to 2 years of drug therapy Combined therapy with its lower incidence of toxicity and delay in development of bacterial resistance has been chiefly responsible for the change It is clearly evident that the overall results are better with prolonged drug therapy It is probably safe to follow the policy of continuing drug therapy for at least 6 months after clinical and laboratory observations indicate that the disease has become inactive The minimal period should probably not be less than 12 months and 2 years seems a reasonable maximum There are patients however with extensive disease not amenable to surgical therapy to whom it may be wise to administer antimicrobial therapy indefinitely

Collapse Therapy This is another area in which older concepts have undergone radical changes At one time statistical studies of pulmonary tuberculosis invariably showed a worse prognosis in patients with open cavities than in those without cavitary disease Large cavities closed occasionally on bed rest alone but usually they did *not* and it was primarily in this type of case that artificial collapse therapy had its greatest usefulness Now

cations for bed rest After the first few weeks when the temperature has returned to normal sufficient rest to avoid fatigue may be all that is necessary Some authorities still maintain a much more conservative attitude insisting on complete bed rest except for bathroom privileges as long as the sputum is positive and chest x rays show continuing changes

With few exceptions treatment should be instituted in a *sanatorium* or in an isolation unit of a general hospital and the patient should remain there for at least a few months The chief advantages of hospitalization are that a careful program of daily activities can be carried out in a neutral environment under expert supervision and the patient s progress can be followed closely with both clinical and laboratory observations Other advantages are that the patient is removed from the community during the infectious period and opportunities for education orientation and rehabilitation are provided

Climate was at one time considered an important part of the treatment of pulmonary tuberculosis but the excellent results obtained in many different environments including hospitals in the busiest portions of our larger cities have made it apparent that climate exerts a relatively insignificant influence on the course of the disease Aside from the elements comprising a good well balanced *diet* no vitamins or other substances are known which specifically promote healing despite the enthusiasm of some for vitamin D ascorbic acid calcium etc The total caloric intake should be designed to enable the patient to regain and maintain his ideal weight

Chemotherapeutic Agents Factors affecting resistance which have been described above are often inadequate by themselves to control tuberculous infection The remarkable effectiveness of drugs in decreasing the number of tubercle bacilli so tips the balance in favor of the host however that many patients are now salvaged who would previously have succumbed to the disease

Three drugs are now in widespread use in the treatment of tuberculosis streptomycin para aminosalicylic acid (PAS) and isoniazid Other agents which may be used when these drugs are poorly tolerated or when bacterial resistance has developed are viomycin and oxytetracycline Viomycin is somewhat less effective than streptomycin and is quite toxic It has proved to be a valuable agent however when isoniazid and streptomycin are poorly tolerated or ineffective Oxytetracycline exerts a weak action but can be used in doses of 2 to 4 Gm daily if necessary as an alternative to PAS Two new drugs pyrazinamide and cycloserine are quite effective but are also toxic Cycloserine is toxic to the central nervous system and pyrazinamide to the liver The principal drugs will be considered separately and then the combinations used in therapy will be described

Either *streptomycin* or its hydrogenated derivative dihydrostreptomycin may be used Streptomycin was at first given alone and was effective for only 2 or 3 months because of the appearance of drug resistant tubercle bacilli It was then learned that the emergence of resistant organisms could be markedly delayed by the concomitant administration of PAS As a result the duration of effective drug therapy has been greatly lengthened For most patients with pulmonary tuberculosis 1 Gm twice weekly has been found to be as effective as the daily administration of the same dose For more serious forms of the disease such as miliary tuberculosis and tuberculous meningitis streptomycin is given every day at least for the first 2 or 3 months

Para aminosalicylic acid commonly referred to as PAS is a relatively weak tuberculostatic agent when used alone but is very effective in delaying the emergence of streptomycin resistant and isoniazid resistant tubercle bacilli The optimal regimen is unknown but the usual procedure is to administer 12 Gm daily by mouth in three or four doses Gastrointestinal irritation is common causing anorexia nausea vomiting and abdominal pain The sodium salt causes fewer reactions than the free acid and is the form of the drug most commonly used To administer 12 Gm of the free acid 16 5 Gm of the sodium salt must be prescribed A lyophilized preparation of the sodium salt is available for parenteral administration and as much as 30 Gm a day can be given intravenously without causing anorexia and nausea Serious toxic reactions are rare Dermatitis and drug fever are encountered occasionally and can usually be controlled by desensitizing the patient with increasing doses of the drug Para aminosalicylic acid is sometimes goitrogenic but thyroid enlargement from this cause can usually be prevented or ameliorated by the administration of desiccated thyroid This is rarely necessary The emergence of drug resistant organisms has been observed when PAS is given alone but is less common when it is administered with streptomycin

Isoniazid a derivative of nicotinic acid is more effective than either streptomycin or PAS in the treatment of experimental and human tuberculosis In contrast to streptomycin it penetrates mononuclear phagocytes and is active against intracellular as well as extracellular tubercle bacilli Like streptomycin isoniazid is bactericidal only against actively multiplying tubercle bacilli Under these conditions Koch Weser has shown that isoniazid is irreversibly bound to the organisms which after several days become non acid fast and lose their

but will serve to illustrate the principles employed and will emphasize the shorter period of hospitalization which is necessary

Following 3 to 6 months of bed rest and chemotherapy the average patient with moderately advanced pulmonary tuberculosis will have attained maximal improvement from an x ray standpoint and cultures of sputum and gastric washings will be negative for tubercle bacilli At this point tomograms are made and if the residual lesions are insignificant in size and extent ambulation is increased This is a gradual process requiring at least 3 months before the patient is up for the whole day Another 3 months is allowed before he returns to work Most patients of this type are discharged from the hospital 6 to 8 months after admission and continue drug therapy on an outpatient basis for at least another 6 to 12 months

If tomograms reveal the presence of cavities or other significant lesions the diseased lung tissue is resected In the type of case under consideration surgery is ordinarily performed between 4 and 8 months after admission to the hospital If the post operative course is uneventful ambulation is begun 2 to 4 weeks later and the subsequent course is as outlined above

This example illustrates the usual procedure in the average uncomplicated case Patients with minimal lesions probably require less therapy and in patients with far advanced bilateral disease the situation is often much more complex and time consuming In such cases the sputum often remains positive and new drugs are added before surgery is performed On the average however the period of hospitalization is much shorter than it formerly was For example in many tuberculosis hospitals the average hospital stay is only 8 months as opposed to 20 months formerly Providing facilities for administering chemotherapy on an outpatient basis is an important feature of the program

Treatment of Special Conditions The general principles underlying the treatment of pulmonary tuberculosis have been described above but the management of certain features deserves special consideration

Hemoptysis Pulmonary hemorrhages are not infrequent in patients with pulmonary tuberculosis and represent a dangerous and alarming complication Fortunately closure of the ulcerated blood vessel occurs promptly in most instances Allaying fears of the patient concerning a possible fatal termination of the episode is an important part of the management of hemoptysis The patient is instructed to lie on the affected side to prevent material laden with bacilli from flowing into other parts of the lungs and spreading the disease If the side from which the blood is coming is not known to the physician from previous examination and x rays the patient often can sense it from a peculiar feeling in one side of the chest Although he lies mostly on the affected side for a few minutes every hour the patient should roll onto the other side so that bloody discharges may drain into the trachea and be removed by gentle coughing The time-honored warning against injudicious use of opiates is sound but small doses of codeine may be a valuable aid in preventing spread of the disease by converting a severe intractable cough into one that is mild but effective The patient usually brings up dark clots of blood over a period of several days as the episode subsides In some instances the bleeding continues or recurs and in such cases it may be necessary to institute artificial pneumothorax, which allows the bleeding vessel to contract and usually terminates the hemorrhage If possible pneumothorax should be avoided since collapsing the lung during the acute episode impairs drainage of the retained secretions and the danger of pleural complications is great If artificial pneumothorax is unsuccessful, phrenemphraxis or pneumoperitoneum is occasionally instituted in an attempt to stop the bleeding If bleeding persists transfusions should be given Many drugs such as calcium gluconate atropine ascorbic acid vitamin K, and nitroglycerin have been thought to be effective in isolated cases of hemoptysis but their general use cannot be recommended Fresh exudative lesions which follow hemoptysis respond extremely well to chemotherapy In many instances of course the exudative "spread" is mostly blood which would disappear on rest alone within a few weeks

Spontaneous Pneumothorax and Bronchopleural Fistula Spontaneous pneumothorax is a relatively common occurrence in young adults It usually begins suddenly with a sharp pain in the anterior chest and in the majority of instances is due to the rupture of a subpleural bulla The bulla may be secondary to fibrosis caused by tuberculosis or other infections or it may be congenital The available evidence indicates that only a small percentage of spontaneous pneumothoraxes are tuberculous in origin and therefore bed rest is not prescribed unless a parenchymal focus is demonstrated or tubercle bacilli are recovered (see p 1381)

When tuberculous in origin, spontaneous pneumothorax results from the ulceration of a subpleural caseous focus or the rupture of a tuberculous cavity directly into the pleural space If possible the lung should be reexpanded at once using catheter drainage with controlled suction for this is a much more serious situation than is the rupture of a bulla In this instance the fistula carries large numbers of tubercle bacilli into the pleural cavity causing infection, fluid formation, and the development of empyema. This may be a

however collapse therapy is indicated in only a small percentage of patients with pulmonary tuberculosis *even when cavities are present* The various forms of collapse therapy will be reviewed briefly and the indications for each will be presented

Pneumoperitoneum This is the only form of collapse therapy which is still used widely and in some leading clinics even this method has been virtually abandoned Administration of air into the peritoneal cavity is simple from a technical standpoint and complications are rare Pneumoperitoneum can be maintained for a long period of time and yet can be abandoned at any time The chief indication is extensive exudative disease with bilateral cavitation In such cases pneumoperitoneum may aid in improving the patient s condition to the point where resection of residual cavities and necrotic foci is feasible In patients unable to withstand surgery refills may be continued indefinitely

Artificial Pneumothorax Designed originally for predominantly unilateral disease with cavitation this form of therapy produced brilliant results in carefully selected cases Because of the high incidence of pleural complications however its use has been virtually abandoned

Phrenemphraxis Temporary paralysis of the diaphragm is effected by crushing the phrenic nerve The diaphragm remains elevated and immobile for 6 or 8 months and then gradually resumes its normal function The main disadvantages of phrenemphraxis are gastrointestinal disturbances especially when it is performed on the left side failure of the nerve to regenerate in about 10 per cent of cases and reduction in respiratory reserve This procedure is rarely used at present

Thoracoplasty Until recently the classic indication for thoracoplasty was chronic fibroid disease at or near the apex of one lung with a cavity which could not be closed effectively or safely by other means Now however surgical excision is performed in the great majority of patients who formerly would have undergone thoracoplasty Primary thoracoplasty is now reserved chiefly for patients with an apical cavity in whom resection is not possible and in whom other measures have failed

Resection It is evident from all that has been said above concerning treatment that surgical resection has become an important part of the management of pulmonary tuberculosis The principal indication for resection is the persistence of open cavities and residual necrotic foci with or without positive sputum following several months of rest and chemotherapy In addition to open cavities solid areas with a diameter greater than 4 cm should probably be resected This problem will be considered in greater detail below in relation to viability of the tubercle bacilli

Following prolonged chemotherapy it is relatively simple to remove small wedges of lung tissue and often several can be resected at one time Little functioning pulmonary tissue is sacrificed and these subsegmental resections can be performed on both lungs With more extensive involvement segmental resection lobectomy or pneumonectomy are indicated Except when lobectomy or pneumonectomy are necessary the mortality rate from surgery should be well under 1 per cent

Bronchopleural fistula and empyema are the most serious problems following resection These can be minimized by deferring surgery until endobronchial disease is well controlled Postoperative spread of the disease formerly a major hazard now occurs in less than 2 per cent of resections If a large amount of lung tissue such as a whole lobe is removed overdistention of the remaining lung tissue may be prevented by performing a thoracoplasty The need for thoracoplasty following lobectomy or even pneumonectomy is open to serious question however and it is now customary to perform the procedure only if signs of overdistention appear several weeks after the resection

Viability of Tubercle Bacilli in Resected Lesions When residual necrotic foci are removed following prolonged chemotherapy they often contain large numbers of tubercle bacilli which appear normal on smear but do not grow on culture media and do not cause disease in guinea pigs This phenomenon was also observed prior to the introduction of chemotherapy and is invariably associated with closed lesions Since the organisms appear normal and healthy the possibility has been raised that they are actually viable but have been so altered by the chemical composition of the closed necrotic lesion that they are incapable of multiplying when subjected to the usual tests Hobby has shown that with appropriate technique growth can often be obtained after many months of incubation in special culture media The need for resecting necrotic foci remains unsettled however since the danger from these metabolically inactive organisms probably decreases with the passage of time Control studies which are still in their early stages do not show a higher incidence of relapse in patients with closed lesions who receive prolonged chemotherapy without surgery Except in clinics where these studies are being carried out only the larger residual necrotic foci (those over 3 or 4 cm in diameter) are routinely resected

Correlation of Rest Chemotherapy, and Resection The manner in which various forms of therapy are correlated especially from the standpoint of time relationships can be considered briefly The statements which are made are somewhat tentative

tive measures mentioned above are unnecessary Pain subsides within a few days and the ulcers heal within a few weeks

Chemotherapy exerts a similarly favorable influence in tuberculous tracheobronchitis Tracheobronchial lesions consist of ulcerations or of granulomatous infiltrations which tend to occlude the bronchial lumen as they undergo fibrosis and healing Stenosing bronchial lesions are to be suspected in the presence of wheezing especially when this is localized over one lung or over a single lobe Episodes of pneumonitis occur distal to the stenosis owing to impairment of the normal drainage of secretions and bronchiectasis may appear in the affected lobe Bronchoscopy aids in determining the nature and extent of the tracheobronchial disease and in assessing the efficacy of antimicrobial therapy Old fibrotic cicatricial stenoses are not benefited by chemotherapy and resection is usually necessary

Generalized Miliary Tuberculosis Resulting from the sudden entry of large numbers of tubercle bacilli into the blood stream miliary tuberculosis is characterized by seeding throughout the tissues of small foci of roughly the same age and size The source of the bacilli is probably in most instances a caseous hilar or mediastinal lymph node which erodes into a blood or lymph vessel Caseous foci in other organs such as the kidneys bones adrenals and prostate may also give rise to massive blood stream invasion Tubercle bacilli are carried to every part of the body but some organs such as the pancreas thyroid skeletal muscles brain and stomach show little or no involvement

Miliary tuberculosis occurs most frequently during the period when the primary complex is active the peak is during early childhood The condition is not rare however in adults The onset may be sudden with high fever aching chilliness and prostration or it may be gradual with an initial period of general malaise and weakness Cough is not a striking feature and if present is usually mild and nonproductive The diagnosis often remains obscure until characteristic miliary lesions appear on the roentgenogram which may not be until several weeks following the onset of symptoms In general when there is an acute onset with high fever and marked prostration the lesions are exudative while in patients with a more insidious onset and low fever a productive reaction is predominant The white blood count may vary from agranulocytosis to marked leukocytosis or there may even be a leukemoid reaction Other conditions which may present a clinical and x ray picture similar to that of miliary tuberculosis are the following

Sarcoidosis
Hemosiderosis
Periarteritis nodosa
Tuberous sclerosis
Lymphangitic carcinomatosis
Silicosis (first and second stage)
Chemical bronchiolitis
Histoplasmosis
Coccidioidomycosis
Bagassosis
Eosinophilic pneumonia (Loeffler s syndrome)
Beryllıosis
Pulmonary adenomatosis
Varicella pneumonitis

Because the lesions are interstitial the recovery of tubercle bacilli is often delayed for many weeks Tubercle bacilli can often be cultured from the bone marrow and sometimes the blood

Heretofore miliary tuberculosis has been a highly fatal condition with death characteristically occurring 6 to 10 weeks following the onset This situation has been altered dramatically by chemotherapy Fever and toxemia usually subside within a few days and within a few weeks the pulmonary lesions begin to show regression In the early days of streptomycin therapy when treatment was continued for only 2 or 3 months over half the cases relapsed and died With prolonged combined chemotherapy recovery occurs in more than 85 per cent of cases and relapses are rare This is one of the forms of tuberculosis in which all three of the antimicrobial agents—isoniazid streptomycin and PAS—are administered simultaneously One gram of streptomycin is injected every day for the first 4 months then twice weekly The daily dosages of isoniazid and PAS are 0 3 to 0 6 Gm and 12 0 Gm respectively Treatment is continued for 2 years

Tuberculous meningitis often occurs during the course of miliary tuberculosis even when the patient is receiving streptomycin therapy Since the addition of ioniazid to the chemotherapeutic regimen however this complication has rarely been observed It is therefore less important to perform frequent lumbar punctures in patients with miliary tuberculosis than it was a few years ago

Subacute and Chronic Hematogenous Tuberculosis Instead of a single massive invasion of the blood stream smaller numbers of tubercle bacilli may escape intermittently into the circulation and give rise to a variety of clinical manifestations Among the more common manifestations are low grade fever local or generalized lymphadenopathy effusions into the pleural and peritoneal cavities splenomegaly and destructive lesions of the bones kidneys skin and eyes

The protean manifestations and bizarre clinical picture caused by subacute and chronic forms of hematogenous tuberculosis provide diagnostic puzzles which often can be solved only by cultures of secretions or discharges or by biopsy of the affected tissues It should be borne in mind that hematogenous foci may remain latent in various organs for many years

simple tuberculous empyema or other organisms such as streptococci and staphylococci may pass through the fistulous opening to form a mixed infection empyema An open bronchopleural fistula with empyema is a dangerous situation the empyema fluid may drain slowly through the fistula into the bronchi and lungs causing widespread dissemination of the disease or if the fistula suddenly enlarges several hundred milliliters of pus may flood into the bronchial tree causing the patient to drown in his own secretions A patent bronchopleural fistula should be suspected when the patient coughs up material similar to pus aspirated from the chest and may be proved by injecting methylene blue into the empyema cavity and subsequently observing the dye in the sputum Once diagnosed a bronchopleural fistula is an indication for surgical drainage because of the dangers mentioned above and because of the failure of mixed infection empyemas to respond to aspiration and irrigations

Tuberculous Empyema This condition is considered separately for its management differs somewhat from that of bronchopleural fistula with mixed infection empyema Pure tuberculous empyema may appear spontaneously or as a complication of artificial pneumothorax or surgical resection There is a tendency to regard all effusions as empyemas if tubercle bacilli can be recovered This is misleading for with clear effusions the prognosis is much more favorable than in true empyemas in which the fluid is thick purulent and swarming with bacilli With chemotherapy aspiration and irrigation and instillation of streptokinase and streptodornase considerable improvement may occur but the empyema is usually not obliterated The procedure of choice at the present time is to excise the entire empyema cavity proceeding extrapleurally as much as possible Diseased lung tissue is resected at the same time To obliterate the space and prevent a recurrence of the empyema a thoracoplasty is usually performed An unroofing procedure of the Schede type which is dangerous and deforming is rarely necessary

Fibrinous and Serofibrinous Pleurisy Pleural involvement occurs in most cases of pulmonary tuberculosis One indication of this is the high incidence of pleural adhesions in patients receiving artificial pneumothorax The adhesions result from localized areas of fibrinous pleurisy overlying peripherally located parenchymal foci and the apposition of the two pleural surfaces aids in localization of the process With fibrinous pleurisy symptoms may be absent or there may be sharp pleuritic pain and a friction rub may be detectable The course of fibrinous pleurisy is usually mild and except for local palliative measures attention should be directed at the underlying parenchymal disease

Five to ten per cent of patients with pulmonary tuberculosis develop serofibrinous pleurisy which is discussed on p 939 Care must be taken to exclude other causes of serous effusions such as pneumonia a careful analysis of clinical signs and symptoms prior to the onset of the effusion is usually adequate to make this differential

Fluid is aspirated initially for diagnosis After removal of most of the effusion 100 ml of air may be injected into the pleural space allowing the remainder of the fluid to fall to the base so that the pulmonary parenchyma can be visualized clearly on the x ray Opinion is divided as to whether repeated aspirations should be performed if the fluid persists and increases in amount after the first tap The author feels that fluid should be removed repeatedly to prevent incarceration of the lung The fluid usually does not reappear after several thoracenteses have been performed and there is a minimal degree of mediastinal shift and pleural thickening It is generally agreed that artificial pneumothorax is contraindicated because the presence of air impedes healing and the lung often does not reexpand after being collapsed for a prolonged period in the presence of fluid

In addition to aspirations the treatment is that prescribed for an active case of minimal tuberculosis namely rest and chemotherapy Isoniazid alone is probably adequate in such cases but most authorities prefer to administer PAS in addition

EXTRAPULMONARY TUBERCULOSIS

Laryngeal and Tracheobronchial Tuberculosis Tuberculous laryngitis usually occurs in patients with advanced pulmonary tuberculosis the infection resulting from the continual passage of bacilliferous sputum over the vocal cords and accessory structures which are irritated by the chronic cough Rarely laryngeal lesions are seen in patients with little or no active pulmonary tuberculosis and the infection then is presumably hematogenous or lymphogenous in origin Hoarseness and a dry sensation in the throat are the common symptoms the diagnosis can be confirmed by direct or indirect laryngoscopy and a biopsy The posterior part of the larynx and vocal cords are first involved and later there are deep extensive ulcerations of the laryngeal cartilages including the epiglottis With the latter there is severe pain on swallowing which interferes with eating Heretofore treatment consisted of complete voice rest cauterization of granulations or deep ulcerations anesthetic sprays to relieve pain and antibiotics to reduce secondary infection With chemotherapy however the condition usually responds so well that most of the pallia

tissues of the pharynx or tonsils has been virtually eliminated but cervical adenitis of lymphohematogenous origin is still observed in both adults and children The swelling usually begins insidiously and may involve one or many nodes The lymph nodes tend to be matted but this is not a reliable diagnostic feature The skin often perforates at one or more sites permitting the drainage of thick greenish yellow pus The treatment of tuberculous cervical adenitis consists of rest and chemotherapy with surgical removal of the residual nodes after several months if they are still enlarged Results with isoniazid and PAS or with isoniazid alone have been so good that surgery usually is unnecessary

Gastrointestinal Tuberculosis Tuberculous ulcers occur occasionally on the tongue lip pharynx and tonsils The diagnosis is made by curetting or excising a small portion of the involved tissue and preparing microscopic sections These lesions respond very well to chemotherapy

Tuberculosis of the esophagus and stomach is rare The *intestine* however especially the lower ileum and cecum is frequently involved in patients with advanced pulmonary tuberculosis as a result of swallowing bacilli The symptoms of ileocecal tuberculosis are variable consisting chiefly of intermittent indigestion colicky pain constipation and diarrhea The appearance of any unusual gastrointestinal complaints should arouse suspicion especially in patients with far advanced pulmonary involvement A moderate anemia is common and should direct attention to the intestinal tract whenever present in patients with pulmonary tuberculosis X ray studies of the ileocecal region provide valuable confirmatory evidence of spasticity and hypermotility The treatment is directed at both the pulmonary lesions and the ulcers in the bowel For the latter a low residue bland diet diminishes irritation of the bowel wall and opium derivatives or bismuth compounds are given to relieve the pain and diarrhea Chemotherapy which is prescribed for the pulmonary disease usually brings about healing of the intestinal lesions In some cases an excessive amount of irritation is caused by PAS and it is wise in most instances therefore to administer streptomycin and isoniazid

Tuberculous Peritonitis This condition results from extension of local lesions in the intestine lymph nodes or genital tract or it may be caused by hematogenous spread from other parts of the body Serofibrinous peritonitis usually has an insidious onset with mild constitutional symptoms and vague intestinal complaints As with serofibrinous pleurisy however the onset may in some cases be acute with high fever severe abdominal pain and marked prostration Fluid often appears especially in the more toxic cases and may require repeated aspirations to relieve distention and discomfort Treatment consists of rest and chemotherapy using the same regimens as for pulmonary tuberculosis As healing occurs thick adhesions may form matting the intestines and omentum together interfering with normal peristalsis and causing stenosis of various portions of the bowel Unless the adhesive process is localized and surgically resectable as it sometimes is in the region of the cecum the treatment is symptomatic and palliative Fortunately this complication is uncommon

Genitourinary Tuberculosis ***Tuberculosis of the Kidney*** In most instances this occurs by hematogenous dissemination from foci in the lungs or lymph nodes occasionally infection may come from the genital tract Small foci may remain latent in the kidneys for long periods before causing destructive lesions many patients with renal tuberculosis show no evidence of active pulmonary disease As the ulcerative lesions in the kidney enlarge tubercle bacilli escape into the urinary tract and often infect the ureters and bladder Dysuria and hematuria are the main symptoms but cases of renal tuberculosis are not infrequently diagnosed before symptoms appear Blood and pus are found in the urine and tubercle bacilli are recovered from the centrifuged sediment by culture or guinea pig inoculation Intravenous and retrograde pyelograms often show characteristic renal ulcerations retrograde studies are particularly helpful in determining whether the involvement is bilateral Lattimer has shown that chemotherapy of renal tuberculosis is so effective that surgery is now rarely necessary Triple drug therapy (isoniazid streptomycin and PAS) was used in his studies and was continued for 1 to 2 years It is now felt that damaged kidney tissue should be removed only if there is a relapse after prolonged drug therapy

Genital Tuberculosis Genital tuberculosis is almost invariably hematogenous in origin and in the male involves the prostate seminal vesicles epididymides and occasionally the testes Infection of the genital tract may in occasional instances be secondary to renal tuberculosis Clinically involvement of the epididymis is diagnosed most frequently although pathologic examinations reveal a higher incidence of tuberculosis of the prostate and seminal vesicles Tuberculous epididymitis often begins insidiously with a gradual development of nodular infiltrations which are moderately tender The onset is sometimes acute with sudden swelling redness and marked tenderness of the epididymis and surrounding structures Rest and chemotherapy are indicated and the epididymis and seminal vesicles are removed only if there are large residual masses of inflammatory tissue

Genital tuberculosis in the female involves the fallopian tubes more frequently than the other

Tuberculous Meningitis As in miliary tuberculosis tuberculous meningitis is more common during early childhood than at any other age period The percentage of adults infected with the tubercle bacillus who die of tuberculous meningitis is relatively small The evidence of Rich indicates that the meninges are infected by direct extension from an adjacent focus In miliary tuberculosis Rich showed that meningitis results not from the direct escape of large numbers of bacilli into the meninges from the blood stream but from miliary meningeal tubercles which gradually enlarge to produce direct extension or that it arises from older dormant foci which became reactivated and extend into the meningeal spaces Pathologically the reaction consists of tubercles edema and congestion and a fibrinous exudate most marked over the base of the brain Various cranial nerves are commonly affected

Tuberculous meningitis may appear in individuals who previously were apparently entirely well The symptoms of miliary tuberculosis usually precede those of tuberculous meningitis by several weeks when the two occur together The early symptoms of tuberculous meningitis are headache restlessness and irritability and on examination typical signs of meningeal irritation are usually elicited The spinal fluid pressure is elevated and there is an increase in protein and cells most of which are mononuclear The chlorides and sugar are depressed moderately in some cases markedly in others On standing a pellicle usually forms Smears of the centrifuged sediment or pellicle may reveal tubercle bacilli but in the majority of cases they do not Repeated cultures and guinea pig inoculations usually are necessary to recover the causative organism

Until streptomycin became available there was no urgency about establishing the diagnosis of tuberculous meningitis treatment was purely supportive and the outcome almost always fatal Now however treatment must be started in many cases before the organisms are recovered Early differentiation between tuberculous meningitis and meningitis due to other agents chiefly fungi and viruses is at times impossible in such cases chemotherapy should be administered if tuberculosis seems the probable cause on the basis of a positive tuberculin test marked depression of the spinal fluid sugar and chloride and the general clinical picture

The treatment of tuberculous meningitis is identical with that outlined above for miliary tuberculosis except that streptomycin should probably be given in daily doses of 2 Gm rather than 1 Gm for the first 4 months Intrathecal administration of streptomycin has been largely abandoned greatly simplifying therapy Intrathecal administration of tuberculin has given dramatic results in some cases but cannot be recommended until the benefits and dangers are more clearly defined Corticosteroids produce a dramatic decrease in fever and toxicity and may diminish the formation of exudate about the base of the brain Their use is probably indicated in most if not all cases these hormones can usually be discontinued by the end of the first month

With the availability of isoniazid the cure rate is in the neighborhood of 80 to 90 per cent in many clinics and poor results occur mostly in patients who are treated late in the course of the disease Many patients make a complete clinical recovery without mental impairment or neurologic defects

Tuberculosis of Lymph Nodes Tuberculosis of hilar and mediastinal nodes which is the commonest form of tuberculous lymphadenitis has its inception during the primary infection when tubercle bacilli escape freely from the initial pulmonary lesion Children with a primary infection may have massive lymph node involvement with few constitutional manifestations The symptoms in such cases are due chiefly to pressure on surrounding structures and consist of wheezing dyspnea and hacking cough In addition compression of a bronchus may cause collapse of one or more lobes with pneumonitis caused by other bacteria distal to the site of narrowing Except when there is perforation into a bronchus or when death results from progressive tuberculosis the involved nodes show a marked tendency to heal and become calcified Even with apparent healing however viable tubercle bacilli may remain in the nodes for long periods Aside from rest and chemotherapy x ray and tuberculin therapy are sometimes recommended but are of questionable value and are potentially dangerous because excessive doses may aggravate tissue necrosis Chemotherapy was at first unimpressive probably because of poor penetration of streptomycin into the large caseous nodes Isoniazid is effective however not only in promoting healing of the mediastinal nodes but in preventing spread to other organs Isoniazid is often used alone in milder cases in children but with extensive involvement streptomycin or PAS should be added Calcified nodes occasionally perforate into a bronchus many years after the primary complex apparently has become arrested This condition known as *broncholithiasis* is characterized by pneumonitis hemoptysis and expectoration of small bits of calcified material

Cervical adenitis or scrofula has become relatively uncommon in the United States in the past 50 years as a result of the elimination of tuberculous cattle and the widespread pasteurization of milk Direct infection by tubercle bacilli through the

marked decrease in the number of domiciliary cases Further advances in therapy can be expected and it is probable that it will eventually be possible to arrest the disease permanently in most patients

One deterrent to this optimistic outlook is the fact that socioeconomic factors are becoming increasingly important Most patients with tuberculosis are among the lower income groups and are individuals who have adjusted themselves poorly to the stresses and strains of modern society The aid of social service workers occupational therapists and psychiatrists is therefore of the greatest importance in the over all plan of rehabilitation

PREVENTION AND ERADICATION OF TUBERCULOSIS

The remarkable decline in the mortality rate from tuberculosis during the first two decades of the twentieth century led a number of careful students of the problem to predict the virtual eradication of the disease by 1950 or earlier The fallacy in the prediction lay in the assumption that the number of individuals harboring active lesions would fall to the point that the disease would cease to propagate itself This has not occurred as pointed out in the section on Prevalence and Incidence the decline in the mortality rate is probably due chiefly to improved living conditions and other factors which tend to increase resistance but the incidence of infection of the population as a whole remains relatively high This means that a large number of individuals with active disease are not hospitalized and remain at large to infect the general populace Evidence indicating the occurrence of such "carriers is provided by the fact that no apparent source of contact can be found for most adults with pulmonary tuberculosis Autopsy studies further indicate that undiagnosed cases of active tuberculosis are common in older people especially males

Preventive measures in addition to the improvement in living conditions which have contributed greatly to the advances accompanying the antituberculosis campaign are earlier diagnosis and treatment isolation of active cases better hospital facilities programs for the rehabilitation of patients with arrested disease to prevent relapse examination of close contacts of tuberculous patients large scale x ray surveys elimination of tuberculous cattle and pasteurization of milk Much has been accomplished but in almost every one of the above categories present efforts and results fall far short of what is desired

BCG (Bacillus Calmette Guerin) an attenuated bovine tubercle bacillus has been used widely abroad for vaccination against tuberculosis Controlled studies of its efficacy are difficult to conduct but the experiments which have been made seem to provide some evidence of its value Protection is by no means complete but a sufficient degree of acquired resistance is conferred to warrant consideration of its use among tuberculin negative groups in which exposure to tuberculosis is especially likely to occur Examples are tuberculin negative nurses medical students and individuals living under poor economic conditions in overcrowded urban areas In many medical and nursing schools the incidence of tuberculosis is so low that the use of BCG has been abandoned

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organs and the lesions are more often unilateral than bilateral Less commonly the ovaries and uterus may be the site of destructive lesions the cervix vagina and labia are rarely affected Vague *irregular lower abdominal pain may be the only* symptom of tuberculous salpingitis and an adnexal mass may be found on pelvic examination If the uterus is involved tubercle bacilli may be present in the vaginal discharge or tuberculous tissue may be removed by curettage The menses may be normal but in advanced cases are usually scanty or absent Tuberculous salpingitis is potentially dangerous because it may cause diffuse peritonitis Again the trend is toward prolonged chemotherapy with surgery only if there are large residual masses

Pericarditis The pericardium can become infected in tuberculosis by discharge of the contents of a caseous mediastinal lymph node into this space by hematogenous dissemination (involvement of serous surfaces by this means is relatively rare) or by direct extension from nearby pleuropulmonary lesions The inflammatory process in the pericardium varies from a serofibrinous reaction containing relatively few bacilli (presumably a response *to sudden discharge of tuberculoprotein onto a* sensitized serous surface similar to that in pleurisy with effusion) to extensive fibrocaseous lesions containing myriads of acid fast organisms

The clinical picture produced by tuberculous infection of the pericardium is extremely variable The sudden onset of substernal pain and fever with accompanying signs such as a to and fro friction rub Ewart s sign etc (see p 1279) in a patient known to have had tuberculosis makes the diagnosis relatively easy However the disease may be entirely asymptomatic attention being drawn to it by the finding of enlargement of the cardiac shadow in a routine x ray of the chest Again because of epicardial and myocardial involvement or tamponade patients may be thought to have congestive heart failure of many etiologies Low grade fever vague complaints of discomfort in the chest and mild weight loss may be the only complaints The finding of pericardial adhesions in many tuberculous patients at autopsy suggests that many instances of minimal pericardial tuberculosis may spontaneously subside and become inactive While occasional patients may accumulate large amounts of fluid in the pericardium sometimes bloody and require repeated aspirations to avoid serious circulatory difficulties this is not usual In such cases there is often simultaneous involvement of one or both pleural spaces leading to confusion with such diseases as systemic lupus erythematosus pyogenic infections and benign idiopathic" pericarditis Occasional patients with tuberculosis of the pericardium run an intermittent course experiencing several bouts of pain and fever with friction rubs reaccumulation of fluid etc

Tuberculosis of the pericardium is the commonest cause of constrictive pericarditis The fibrosis and *calcification that accompany the healing process in* this infection can lead to encasement of the heart in an unyielding tunic of dense scar with serious effects upon the circulation (ee p 1282)

Diagnosis by demonstration of tubercle bacilli in smears or cultures of aspirated fluid is often difficult and in cases of doubtful etiology pericardial biopsy is becoming an increasingly feasible and useful procedure The institution of chemotherapy of the type recommended for pulmonary tuberculosis before operation makes spread of infection unlikely It is not uncommon to find a surprising amount of pericardial scar when operation for biopsy is carried out and in such instances many feel that pericardiectomy can and should be done The final place of early surgical treatment in tuberculous pericarditis remains to be determined It is clear however that in some cases where infection is arrested or eradicated by chemotherapy sufficient mechanical difficulty can remain to warrant *excision of the thickened membrane* The duration of drug treatment should be at least a year and indications for rest proper diet etc differ in no way from those in other forms of tuberculosis

Skeletal Tuberculosis Bone and joint tuberculosis is usually hematogenous in origin and is most likely to occur in young children In adults the incidence is higher in males and it is more frequent in Negroes than in whites With joint involvement diagnosis depends on study of aspirated fluid or pus and on surgical biopsy Destructive bone changes visible on roentgenograms often occur late In over half the cases there is active pulmonary tuberculosis and a presumptive diagnosis can often be made on this basis

Chemotherapy if started early often results in a complete return of function of the involved joints With marked bone destruction surgical immobilization (arthodesis) is usually necessary but this is carried out only after a period of drug therapy Triple drug regimens similar to those used for genitourinary tuberculosis should be employed Details of orthopedic procedures are beyond the scope of this presentation Close cooperation between the internist and orthopedist is obviously desirable

PROGNOSIS

The outlook for the great majority of patients with tuberculosis has been vastly improved by the availability of effective chemotherapeutic agents and advances in surgical management The case fatality rate is falling rapidly and there has been a

contacts never exhibiting clinical disease may play a role in transmission If so the incubation period may not be so long as currently suspected

Pathologic Anatomy The lesions may be classified according to their microscopic appearance This leads to the recognition of four principal types (1) the lepromatous (2) the tuberculoid (3) the dimorphous and (4) the indeterminate

In the *lepromatous type* bacilli are numerous they multiply intracellularly there is little cellular response and little evidence of resistance to the disease The cutaneous lesions are usually numerous are symmetric in distribution and take the form of nodules papules macules and diffuse infiltrations Most characteristic is the appearance of the leproma or nodule It is distinguished by the lepra cell" a large macrophage containing numerous bacilli and fat droplets In large accumulations bacilli form globi and rosettes

The *tuberculoid* lesions are observed in cutaneous leprids and the affected nerves The leprids are often macules and are usually asymmetric in distribution Bacilli are few or absent and epithelioid cells giant cells lymphocytes and plasma cells are present often in the form of tubercles

The *dimorphous* lesion which is uncommon and presumably represents a transient state has microscopic features of both the lepromatous and tuberculoid forms

The *indeterminate type* of lesion contains few bacilli and shows a slight cellular reaction which is limited to the perivascular and perineural areas The gross lesions in the skin and nerves are not characteristic or advanced enough to permit classification with the two principal clinical types

Clinical Classification A combined clinicopathologic classification is recommended since it makes more direct clinical immunologic bacteriologic and epidemiologic correlations possible That is regardless of the sites involved the lepromatous type is characterized by a relatively rapid course a negative lepromin reaction and lesions containing many bacilli and because of this is an "open or dangerous type for the community The tuberculoid type has a more chronic course shows more resistance to the disease has a positive lepromin reaction has few bacilli in the lesions and is therefore a closed type and less of a community hazard The indeterminate type is viewed as a transitional form The lepromin reaction in this type has prognostic significance since many cases with negative reactions develop into the lepromatous type and those with positive reactions into the tuberculoid type The dimorphous type is a macular lesion not representative of a particular clinical group

The distribution of types varies in different geographic areas The tuberculoid type is often preponderant in areas known to have had leprosy for long periods and where control has shown some degree of effectiveness the lepromatous type may predominate in newly involved areas and those in which control has been less effective

Clinical Course The onset is often unheralded and difficult to date The incubation period averages about 3 to 5 years Claims of very long incubation periods must be scrutinized since minor lesions are likely to remain unrecognized for long periods

Initial skin lesions of the lepromatous type usually are found on the extensor surfaces the forehead cheeks and ears Their development may be so gradual that the changes may be noted by others before the patient himself is aware of them

Early signs of mucosal involvement in the upper respiratory and intestinal tracts may be evidenced by nasal discharge dysphagia and hoarseness and dyspnea due to laryngitis

The patient with the tuberculoid type is more likely to be aware of the disease early The initial lesions usually take the form of hypopigmented or erythematous anesthetic macules Subjective manifestations due to neural involvement consist of numbness tingling and formication and the skin may show burns or other lesions which the patient states are painless

The progressing cutaneous leprids of tuberculoid leprosy enlarge and clear centrally The central area is anhidrotic and anesthetic to light touch pain, and thermal stimuli The nerves later are thickened and tender if the disease progresses Before nerve destruction and atrophy occur pain of a neuritic type may be prominent Late stages are characterized by resorption of the small distal bones of the hands and feet and painless ulcers of the extremities

Although more marked in lepromatous leprosy generalized lymph node enlargement is common in all types of leprosy

The lepromin skin test is primarily of prognostic value The test material is prepared from lepromatous nodules Those with tuberculoid leprosy generally show positive reactions and lepromatous cases negative reactions A satisfactory therapeutic response is shown by the transformation of a negative to a positive reaction in the lepromatous type Those patients with the indeterminate type of lesion who have positive lepromin tests are likely to develop tuberculoid lesions if the disease progresses and those who have negative lepromin reactions lepromatous lesions

Recent studies have defined better the relationship between tuberculosis and leprosy The guinea pig normally lepromin negative becomes lepromin positive after BCG (Bacillus Calmette Guerin) administration Patients who have remained lepromin negative after sulfone treatment may become lepromin positive following BCG ad

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142 LEPROSY (Hansen's Disease)

Gustave J Dammin

Definition Leprosy is a specific infectious disease of man caused by the *Mycobacterium leprae* It is usually characterized by a long incubation period a long course with exacerbations and remissions and involvement primarily of the skin and mucous membranes and/or the peripheral nervous system The major forms of the disease are the polar forms the lepromatous and the tuberculoid in addition there are dimorphous and indeterminate forms

History Whether leprosy as it is understood today was described in the ancient records has been questioned (Lendrum) In Europe leprosy appeared first in Greece in the fourth century B C probably having been introduced from the East It spread northward and westward and had affected most of Europe by the end of the tenth century A D Leprosy was prevalent in Europe until the fourteenth century and then began slowly to decline

As leprosy was declining in Europe it was being spread to the Western Hemisphere by the slave traders and the discoverers from Portugal and Spain In the United States leprosy appeared first in Louisiana in 1758 presumably spread from the West Indies Additional foci were established from other sources in Minnesota from Norway in California and Hawaii from China and India

Etiology *Mycobacterium leprae* described by Hansen in 1874 is accepted as the causal agent in human leprosy even though the organism has not been cultivated and attempts to transmit leprosy to animals or man have not been successful (Hansen)

Mycobacterium leprae is a pleomorphic acid fast non spore forming gram positive bacillus Lepra bacilli differ from tubercle bacilli in that they (1) are found in tremendous numbers in lesions (lepromatous) in the form of packets palisades and globular masses (globi) both intra and extracellularly (2) decolorize more readily (3) may be stained with the stronger bacterial stains (4) cannot be cultivated and do not produce disease in animals following inoculation

Epidemiology and Pathogenesis The exact mode of transmission is not known A history of prolonged direct contact usually beginning in childhood is common Leprosy may not manifest itself clinically until 1 to 5 years after the period of exposure and appears most often during the third decade of life Resistance to leprosy appears to increase with age

Leprosy is not transmitted to the offspring and it is well known that infants born of leprous parents if removed and reared in an environment permitting no contact do not develop the disease Those not separated are likely to develop leprosy in early life even when separated at six months of age 50 per cent of the children had clinical manifestations by the age of five years

Of interest are cases recognized as accidental inoculation leprosy One report concerns two marines who were tattooed successively by the same man in Melbourne Australia on the same day in June 1943 Both developed maculoanesthetic leprosy in the tattoos about 2½ years later (Porritt and Olsen)

Lepra bacilli leave the body by many routes In lepromatous leprosy they may escape in the secretions and excretions and through any interruption in the involved skin and mucous membranes The route by which they enter a new host is not known but it is believed that infection occurs by way of the skin and mucous membranes following direct contact

Once in the body the bacilli are probably spread by way of the lymphatics and blood stream and by autoinoculation Localization occurs primarily in the skin and/or nerves and in advanced cases of lepromatous leprosy bacilli are found in many of the viscera Bacillemia occurs more commonly in the lepromatous type

The problem of the carrier state is important and only recently under study It appears possible that

3 to 4 years and some approximately 20 per cent of all clinical cases will show no recognizable improvement

The thiosemicarbazones are *not so effective* as DDS but are occasionally useful as alternative agents The response to isoniazid has been poor in most cases ACTH and cortisone have been found to produce desirable temporary effects but unfortunately have been followed by aggravation of neural and cutaneous lesions Their use is justified *in treatment of the drug fever induced by sulfones* In leprous ophthalmitis cortisone applied locally is advised (Lowe)

Prognosis This is dependent upon the type of leprosy the stage in which treatment is begun and the general health of the patient The occurrence of temporary and occasionally permanent spontaneous disease arrest must be kept in mind The tuberculoid type has a relatively better expectancy although disability is common and the prognosis is relatively better in so far as disease arrest is concerned The lepromatous type has the *poorer outlook With the hope which the sulfone* derivatives hold it should become easier to induce patients to seek treatment earlier Generally pneumonia and tuberculosis are common causes of death In the United States over one third of the cases die with renal insufficiency due to amyloidosis The average duration of life after diagnosis is 20 years and the average age at death is fifty nine years

Control Segregation and early treatment of patients particularly those with the lepromatous type are essential *A program of control should be directed toward encouraging voluntary admission to* a leprosarium The harm the patient may do to himself and his immediate contacts by delaying treatment and the hopefulness with which treatment can now be regarded should be emphasized *Mention has been made of the enlarging role which* mass BCG vaccination has been given in control Efforts to identify and define the carrier state should be intensified and the efficacy of the sulfones in controlling the carrier determined Cultivation of a more objective and less emotional public attitude toward the disease is fundamental to any control program

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ministration In some instances clinical improvement has accompanied this change The place of BCG in the treatment of leprosy is yet to be defined but its contribution to control has been accepted in many countries and particularly where tuberculosis is common BCG vaccination in children results in most instances in positive early or Fernandez reactions and late or Mitsuda reactions

The histamine test may be of assistance when the skin lesions are atypical or the neurologic examination cannot be satisfactorily performed The normal cutaneous response to a needle prick through a drop of 1 1 000 histamine consists of a wheal with surrounding erythema When there is impairment of neural function in leprosy only the wheal and no erythematous halo appears

The pilocarpine test showing impairment of the sweating response to intradermally injected pilocarpine is helpful in identification of the leprid

Laboratory Diagnosis Although clinical findings may be sufficient for diagnosis demonstration of the bacilli or the histologic lesion is desirable for confirmation or to observe response to therapy In searching for bacilli in a suspected lepromatous case in which the skin lesions are not distinctive the ear lobule should be examined The lobule is held firmly enough to cause blanching A small incision is made with a sharp scalpel and the material which can be scraped from the edges is spread on a slide Stained by the Ziehl Neelsen or fuchsin method a positive lesion will show numerous acid fast bacilli In suspected tuberculoid leprosy a biopsy is usually necessary

The erythrocyte sedimentation rate is elevated in all types of leprosy but is most increased in the lepromatous type Serologic tests for syphilis performed with the beef heart antigens may be positive in 10 to 40 per cent of cases of leprosy whereas with cardiolipin antigens only 1 to 2 per cent may be positive TPI (*Treponema pallidum* immobilization) tests have been negative in most cases of leprosy unless syphilis also was suspected The beta globulin C reactive protein is present in most cases of active leprosy and absent in most cases of arrested leprosy (Rabson)

Differential Diagnosis In nonendemic areas leprosy is seldom diagnosed early Once leprosy is suspected clinical and laboratory procedures are usually successful in establishing the presence or absence of the disease It must be differentiated from syphilis superficial fungous infections lupus vulgaris lupus erythematosus vitiligo dermal leishmaniasis yaws seborrheic dermatitis psoriasis Boeck s sarcoid rheumatoid arthritis nonspecific neuritis syringomyelia and neurofibromatosis Differentiation from syphilis may be difficult because of clinical similarity and the frequent appearance of positive serologic tests for syphilis in leprosy Important procedures in differential diagnosis are (1) the examination of cutaneous and mucosal lesions for *M leprae* (2) study of skin sensation and reaction to histamine and pilocarpine and (3) examination of the peripheral nerves for thickening and tenderness

Treatment Several considerations must be heeded in evaluating the efficacy of therapy Firstly leprosy is an intermittently progressive chronic disease during which temporary and even permanent spontaneous arrest can occur Secondly the patient seeks treatment during and toward the end of an exacerbation which may naturally be followed by a remission of variable duration Thirdly the initial appearance of an exacerbation may be precipitated by a more or less self limited disease—e g malaria or dysentery—or by an unfavorable nutritional and hygienic state which when corrected may be followed by a remission Clinical and laboratory observation over a period of years is therefore necessary for proper evaluation of therapy

The general therapeutic regimen should resemble that for tuberculosis since much can be accomplished by good diet and regulated rest and exercise Chaulmoogra (hydnocarpus) oil was long used in Asia in the treatment of leprosy but only during the latter part of the nineteenth century was it introduced into Western medicine The Cairo Congress in 1938 regarded chaulmoogra oil and its esters as the most efficacious drugs for the treatment of leprosy Although many cases appeared to be benefited this opinion was not concurred in generally

The sulfone Promin was first used for the treatment of leprosy in 1941 at the Carville National Leprosarium

More recent years have seen the emergence of the sulfones as the most efficacious drugs in the treatment of leprosy Most success has been obtained with the parent sulfone 4 4 diaminodiphenylsulfone (DDS) It is rapidly absorbed after oral administration and slowly excreted cumulative effects therefore occurring when large doses are given Initially 100 mg is given orally twice a week and the dose increased by the same amount each week until the dose of 400 mg twice a week is reached This amount is continued and the patient is observed for toxic effects such as hemolytic anemia hepatitis drug fever dermatitis and psychosis Muir has reported that vitamin B_1 increases the tolerance for DDS

The response to therapy is estimated by periodic bacteriologic examinations and objective clinical studies Early cases and those with low bacteriologic indices can be expected to show improvement after about 1 year of treatment others may require

the urinary tract) and special features of the tissue reaction produced by some bacterial species make *it possible to recognize* infection by them with considerable accuracy The *staphylococci* produce rapid necrosis and early suppuration with large amounts of creamy yellow pus (see p 840) Group A beta hemolytic streptococcal infections (p 849) tend *to spread rapidly through tissues causing intense* inflammatory edema and striking erythema but relatively little necrosis and thin serumlike exudates anaerobic streptococci (p 869) and members of the *Bacteroides* group (p 881) produce necrosis and profuse brownish foul smelling pus *Pseudomonas* infections (p 880) are often rather indolent and their thick bluish green exudate is familiar to most clinicians *the pneumococcus* (p 833) stimulates the production of viscid greenish pus containing large plaques of fibrin and denatured protein

The causative agents of many other diseases are *capable of producing localized infection in tissues* that are not usually involved in the specific "clinical entities ascribed to them Examples include the typhoid bacillus *Corynebacterium diphtheriae* (cutaneous ulcers) *Brucella Pasteurella tularensis* and *many others*

The identification of the infecting organism or organisms is an important procedure in the choice of local or *systemic chemotherapy and should not* be neglected However when one is dealing with infection in an area where exposure to the micro flora of the body is constant (sputum paranasal sinusitis cutaneous ulcers) it is unlikely that cultures will ever *become sterile* and the interpretation of the findings in serial cultures during therapy must be tempered by this realization

Pathogenesis Factors predisposing to the initiation and persistence of infection in a tissue include trauma *obstruction of normal* drainage (*sweat* glands biliary tract bronchial tree urinary tract) ischemia *(infarction gangrene) chemical irritants* (gastric contents bile intramuscularly injected drugs) hematoma formation accumulation of fluid (lymphatic obstruction *cardiac edema*) *foreign* bodies (bullets splinters sutures) and others such as the occurrence of turbulence in the vascular system (see Bacterial Endocarditis p 971)

Infection in soft tissue usually begins as a *cellulitis* a diffuse acute inflammation with hyperemia edema and leukocytic infiltration but little or no necrosis and suppuration With some organisms this is followed by necrosis liquefaction accumulation of leukocytes and debris suppuration loculation and walling off of the pus and formation of one or more *abscesses* Abscess formation is particularly *prone to follow* infection in a preexisting circumscribed space or cavity examples being the fallopian tubes lung cysts and pilonidal sinuses

Ureteral obstruction in the presence of pyelonephritis is sometimes followed by accumulation of large quantities of thick pus in the renal pelvis a *pyonephrosis*

The local spread *of infection generally follows* the path of least resistance along fascial planes proper surgical treatment is based upon a knowl*edge of these routes which will be described for* specific infections later in this chapter Lymphatic spread can lead to lymphangitis lymphadenitis or if the regional nodes suppurate to the formation of a *bubo* Involvement of local venules or large veins can lead *to infective thrombophlebitis with* resulting bacteremia septic embolization and systemic dissemination of infection Staphylococci streptococci and *Bacteroides* are notorious for the frequency with which they produce vascular lesions of this type

Depending upon the infecting organism and the anatomy of the affected region a small abscess may *subside completely there may be gradual encapsul*ation of the accumulated pus and persistence of the focus in a chronic or quiescent state or the lesion may point and rupture into adjacent tissues or to the outside surface of the body as usually hap*pens with furuncles and occasionally with pleural* abscess (*empyema necessitatis*) Spontaneous drainage of the pus to the outside ordinarily leads to subsidence and healing of a superficially situated suppurative focus However if the abscess is deeply situated and *well encapsulated there is often per*sistence of a fistulous tract and the formation of a chronic draining sinus *The development of persistent sinuses over an area of suppuration produced by ordinary pyogenic bacteria should always suggest involvement of underlying bone or the presence of a foreign body* Fistulas that open onto the skin are of course soon colonized by microorganisms *from the external environment* Ordinary bacterial cultures of drainage fluid almost invariably show a *mixed flora and should never be relied upon for the* etiologic diagnosis of the underlying disease This is particularly important when one considers those *disorders that characteristically lead to persistent* sinus formation tuberculosis mycotic infection (actinomycosis blastomycosis) melioidosis glanders tularemia and rarely amebic abscess of the liver or cecum

Therapeutic Considerations *Recognition of the* subsidence of inflammation and striking symptomatic improvement that follow spontaneous evacuation of a suppurative focus led long ago to the adoption of *surgical incision* for the treatment of abscesses The exact *reasons for the amel*ioration of local and constitutional manifestations that results from drainage of pus are still unknown but clinically the benefits of adequate incision and drainage are unequivocal

Section 9 Infections of Specific Tissues and Anatomic Sites

Ivan L Bennett, Jr

It is traditional and convenient to classify bacterial diseases in terms of etiologic agents This is adequate for those that follow more or less consistent patterns as do typhoid anthrax brucellosis tularemia or tetanus but there are other important disorders that lend themselves poorly to categorization on the basis of causative organisms Because many microbial agents are able to invade and to localize in almost any tissue they are not regularly associated with a single symptom complex Furthermore infection of an anatomic site such as the urinary tract or the meninges by any one of a wide variety of unrelated bacterial species produces essentially the same symptoms and clinical signs Recognition of the basic pathologic process by the clinician is in most instances independent of microbiological techniques This statement is not intended to direct emphasis away from the important procedure of specific identification of infecting bacteria as a basis for choosing the appropriate antimicrobial drugs

In this section many clinical entities are described Several are more likely to be caused by certain microorganisms than others but all can be *produced by many species Most can be recognized* in their typical forms by history physical examination and clinical tests of blood and urine Final identification of the infecting agent may depend upon time consuming bacteriologic tests but a knowledge of the likely pathogens often enables the physician to initiate appropriate therapy before this information is available Surgical drainage is an essential part of proper management for several of the disorders to be described indeed surgery may be an emergency procedure for many of them necessitated not by the species of the infecting organisms but by the anatomic location of the infection

For these reasons it seems logical to describe these afflictions in terms of their manifestations in the patient Cross references to other sections of the book for details of bacteriology have been given where specific causative agents are mentioned for the diseases

143 LOCALIZED INFECTIONS AND ABSCESSES

Ivan L Bennett Jr

Localized pyogenic infection can develop in any region or organ of the body This may be initiated by *trauma* and secondary bacterial contamination by some *alteration in local conditions* that renders a tissue susceptible to organisms already present as part of the normal flora to which it is ordinarily immune by *contiguous spread* from a nearby lesion or by *metastatic implantation* of microorganisms *carried in blood or lymph*

Infection is more likely to occur in some anatomic sites than in others because of structural differences favoring localization or because of greater exposure to the risk of trauma (for example the hand)

The symptoms and signs of infection in several areas are characteristic enough to allow their clinical recognition and also to enable one to predict the pathways likely to be traversed as adjacent or distant structures become involved The definite treatment of many circumscribed infections particularly if abscess formation occurs is primarily surgical Several however are *complications of* diseases that are ordinarily cared for by the internist and the treatment of any of the serious types may call for careful integration of medical and surgical measures It is important therefore that the physician be able to recognize the major types of localized suppurative disease and know something of the principles of their management

Etiology Under appropriate conditions of lowered tissue resistance almost any of the common bacteria can initiate the infectious process Cultures from open lesions such as those of the skin or from intraabdominal foci arising from perforations of the gastrointestinal tract frequently contain several bacterial species as might be expected the organisms found most frequently are the normal flora of these regions

Infection in certain areas is more likely to be caused by certain organisms (examples being staphylococci in the skin and coliform bacteria in

interfere Abdominal or pelvic examination under anesthesia is sometimes useful in these circumstances

Auscultation may reveal a friction rub over an abdominal viscus the pleura or the pericardium The rapid development of an effusion in the pericardium pleura abdomen or a joint should suggest infection Similarly fluid detected by transillumination of paranasal sinuses or inspection of the tympanic membrane can be the first sign of infection

Depending upon the location of an abscess symptoms and signs referable to encroachment upon adjacent structures may dominate the picture Respiratory obstruction may be the first sign of mediastinal abscess dysphagia often first calls attention to peritonsillar or retropharyngeal abscesses and acute tamponade is sometimes the initial clue to pericardial infection Localizing signs of dysfunction are especially striking and important with suppurations of the brain and spinal cord (see p 975)

Local pain and tenderness or signs of dysfunction are relatively mild or equivocal in some patients *constitutional manifestations of fever prostration and weight loss* dominating the picture The fever can be low grade but is often hectic with repeated rigors and drenching night sweats Fatigue and anemia are frequent and weight loss may be so rapid as to result in emaciation within a few weeks A patient with these symptoms and signs may have chronic subphrenic perinephric or other abscess in the complete absence of any detectable physical sign pointing to the location of a huge accumulation of pus

Fluctuation of a mass on palpation is a reliable sign that it contains fluid perhaps pus but failure to detect this sign when deeper structures are examined is no guarantee that suppuration is absent and should not be taken by itself to indicate that the mass is noninfectious in origin or that drainage is not required

Laboratory Findings Peripheral polymorphonuclear leukocytosis is frequent with abscesses and unexplained elevation of the white count in any patient should lead to a search for localized suppuration Depending upon the severity and duration of infection there may be a chronic normocytic normochromic anemia Mild albuminuria is occasionally noted in febrile patients and has no diagnostic import

Pus or fluid obtained by needle aspiration or incision of a suspected lesion should *always* be stained and examined directly in addition to being cultured aerobically and anaerobically As has been mentioned pus is a poor metabolic substrate for many bacteria and organisms may fail to grow in cultures particularly from an abscess of long standing In such instances the findings on microscopic examination may be the only guide in choosing proper chemotherapy for the disease

Blood cultures are often positive in intravascular infections such as endocarditis (p 970) in pyelonephritis (p 967) and in pyogenic infections in which localized abscesses are metastatic as in staphylococcal (p 839) streptococcal (p 845) and *Salmonella* (p 888) bacteremias It should be remembered that manipulation including surgical incision of any localized infection can be followed by transient bacteremia

CLINICAL FEATURES OF INFECTIONS IN VARIOUS REGIONS

The pathogenesis diagnosis and treatment of several important infections in specific anatomic sites and organs are discussed in detail in other parts of this book These include lung abscess (p 1394) mediastinitis (p 1373) bacterial endocarditis (p 970) pericarditis (p 1281) infections of the brain and spinal cord (p 970) osteomyelitis (p 841) pyelonephritis (p 970) appendicitis and appendiceal abscess (p 1455) pylephlebitis and hepatic abscess (p 1518) pancreatic abscess (p 1477) and diverticulitis (p 1465)

The remainder of this chapter is devoted to some features of dermal infection chronic ulcerations and a consideration of a number of other important regional infections including those of the neck spleen subphrenic space kidney perirenal space retroperitoneal space and rectum

Skin and Subcutaneous Tissues

Impetigo is a superficial infection caused by hemolytic staphylococci and Group A hemolytic streptococci It is primarily a disease of children common in warm weather characterized by multiple erythematous lesions which vesiculate and are intensely pruritic Local spread occurs through scratching and release of infected vesicle fluid Serious complications are metastatic abscesses and hemorrhagic nephritis (p 863) Treatment consists of local and general cleansing of the skin application of bacitracin neomycin ointment covering with a loose dressing to prevent further contamination and appropriate systemic antibiotics

Deeper infections of the skin are almost invariably staphylococcal in origin and are described in the chapter beginning on p 839 Erysipelas a characteristic dermal lesion produced by Group A streptococci is described on p 854 and erysipeloid is described on p 918

Lymphadenitis with or without suppuration can complicate any pyogenic skin lesion and is often striking with superficial streptococcal infections

It has been learned by experience that incision of infected tissue before the stage of liquefaction and accumulation of pus is well established is often deleterious failing to relieve discomfort and facilitating spread of infection For this reason it is sometimes necessary to wait until an abscess ripens that is localizes and comes to a head It has long been known that the *application of heat* to an area of inflammation will relieve pain and often speed the subsidence of cellulitis without suppuration If necrosis of tissue is already under way hot applications appear to facilitate localization of the process and accumulation of pus making incision and drainage feasible at an earlier time Another procedure that aids in reduction of swelling and relief of pain is *elevation of the affected part*

The availability of specific chemotherapeutic drugs has modified the need for heat elevation and incision surprisingly little The early administration of sulfonamides or antibiotics has reduced the incidence of suppurative complications in many disorders but once suppuration has appeared antimicrobial drugs become remarkably incapable of eradicating the infecting organisms It is known that pus contains substances which effectively inactivate the sulfonamides and this fact alone accounts adequately for the failure of these drugs to influence localized suppurations

Antibiotics however can be demonstrated in vitro to retain their antibacterial activity in the presence of pus and necrotic tissue and the explanation of the deleterious effect of suppuration upon their therapeutic effectiveness is not simple Several factors undoubtedly contribute to the final result It is probable that failure of the drug to penetrate into an area of suppuration is rarely the reason for therapeutic failure although this possibility exists in such infections as osteomyelitis it is usually overcome by increasing dosage Because direct instillation of the antibiotic into an infected area is not by itself a curative procedure other factors are probably more important than faulty diffusion of the agent into the focus The experiments of Eagle and of Wood have shown clearly that an established inflammatory exudate is a relatively poor environment for bacterial multiplication Because penicillin s bactericidal action is exerted only against rapidly multiplying organisms it is now believed that failure of this antibiotic to eradicate bacteria in an abscess is related to their *relatively inactive metabolic state* Because a bacteriostatic agent such as tetracycline or chloramphenicol is capable only of inhibiting multiplication of bacteria and usually exerts no direct lethal action the final death of organisms in any infection treated with agents of this type is dependent upon other mechanisms For most pyogenic bacteria *phagocytosis is one of the most important* of these mechanisms (although there must be others that have not been as carefully studied) and it is now known that in the absence of phagocytes or in circumstances which inhibit their activity bacteriostatic drugs are relatively ineffective In fluid filled cavities and particularly *in the metabolically unfavorable* milieu of an abscess phagocytosis is greatly reduced and consequently despite inhibition of multiplication bacteria can remain dormant and survive for long periods of time It is probably a combination of these two circumstances decreased multiplication of bacteria and decreased phagocytosis that makes infection on the heart valves in the kidney or in the meninges as well as soft tissue abscesses so resistant to antibiotic therapy Administration of large doses of bactericidal drugs for long periods often becomes necessary to achieve cure

From a practical viewpoint antimicrobial drugs can be expected to prevent suppuration if given early enough or to prevent spread of an already existent abscess but they cannot be substituted for surgical drainage Indeed their use in the face of a lesion requiring evacuation of pus is one of the most common serious errors in treating infections

In thoracic empyema suppurative pericarditis or pyarthrosis excellent therapeutic results are sometimes achieved by aspiration of pus through a needle and instillation of antibiotics into the infected area The success of this procedure however *is fully as dependent upon the adequacy of the* drainage that it achieves as it is upon the local application of the antibiotic and if there is loculation or the exudate becomes too viscid to allow removal surgical incision becomes mandatory

In the presence of infective thrombophlebitis surgical interruption of the veins by ligation or in certain instances by total excision of an infected segment is often indicated to prevent seeding of other organs by infected emboli

Manifestations Secondary infection of wounds and cutaneous ulcers is usually recognizable by inspection Infections of the skin and subcutaneous tissues almost invariably produce the classic manifestations *redness tenderness heat* and *swelling* Reddish streaks extending proximally and associated with tender enlargement of regional lymph nodes indicate lymphangitis Systemic symptoms can be absent or mild or there can be fever *malaise prostration* and leukocytosis

Infection and suppuration in deeper tissues or in body cavities is often manifested by local pain and tenderness but the task of locating and determining the exact nature of the lesion can be difficult The palpation of a tender mass is helpful but muscle spasm and intervening structures often

systemically or locally administered antimicrobial drugs the predominating bacterial species show great variation when lesions are cultured serially Particularly noteworthy is the replacement of sensitive organisms by resistant strains or species in the course of chemotherapy

Treatment of chronic dermal ulcers should be directed toward the underlying disorder but should also include *local debridement* and *chemotherapy* Debridement by surgical excision is often needed but the local application of proteolytic enzymes such as Varidase a mixture of streptokinase and streptodornase or trypsin so called "chemical or medical debridement is sometimes sufficient Intensive systemic administration of antibiotics should be carried out only in conjunction with definitive surgical procedures or when infection can be controlled in no other way but the prevention of infection by prophylactic administration of antimicrobial drugs is a hopeless task The result will be the development of a flora resistant to the drugs being used The *local application of antibiotics* is sometimes highly effective and it is in the management of chronic mixed infections of this type that several potent but toxic antibiotics have great value The topical use of an ointment or solution containing neomycin bacitracin and polymyxin results in a bactericidal effect against a wide variety of organisms and will sometimes temporarily sterilize a chronic lesion Other useful topical medications are Furacin and 3 per cent acetic acid the latter being especially helpful in *Pseudomonas* infections

Infections of the Head and Neck

Mention may first be made of the peculiar danger of pustules of the nose and upper lip because of the likelihood of extension of infection intracranially through the angular vein to the cavernous sinus (see p 978) Such lesions should be treated conservatively manipulation or incision being avoided if possible and systemic antibiotics being given if local swelling or redness appears

Suppurative parotitis is usually a complication of chronic debilitating disease or blockage of Stensen s duct by a calculus and is largely avoidable by maintenance of hydration and oral hygiene Its onset is heralded by local pain and swelling fever and chills are frequent Frank pus can sometimes be expressed from the duct and the gland itself is firm and tender often with pitting edema of the overlying skin In severe cases there may be facial palsy on the involved side Removal of any obstruction in the duct application of heat and administration of antibiotics sometimes leads to prompt subsidence of local and systemic signs However incision is still required in many cases and *failure of a patient to respond promptly to these more conservative measures is an indication for surgical drainage* Abscess formation may be far advanced without there being detectable fluctuation because of the dense fibrous capsule of the gland Before chemotherapy was available the mortality rate in pyogenic parotitis was 30 to 50 per cent

The use of penicillin and other antibiotics has reduced the incidence of many formerly common suppurative complications of streptococcal pharyngitis (see p 845) However as a result of streptococcal sore throat *Bacteroides* infections of the pharynx (see p 882) or introduction of infection by trauma to the floor of the mouth or the pharyngeal wall abscesses of the deep cervical structures still occur *Suppurative cervical adenitis* once an all too common sequel to streptococcal pharyngitis in children is now rare *Peritonsillar abscess* or *quinsy* is manifested by fever sore throat unilateral pain radiating to the ear on swallowing and enlargement of the tonsil with redness and swelling of the adjacent soft palate Treatment with penicillin and irrigations of warm saline sometimes leads to subsidence of the process but if digital palpation reveals fluctuation surgical drainage with or without tonsillectomy is indicated

The course of *deep cervical infections* is fully as dependent upon the anatomical arrangement of fascial planes as is that of infections of the hand There are five important potential compartments in the anterior neck these are described in detail in the article by Barnhill listed at the end of the chapter Infection in any of these areas is serious and attended by fever prostration and leukocytosis A tender mass may be palpated but it is to be emphasized that *surgical evacuation of such an infection should not be delayed because of failure to detect fluctuation* which is usually absent because of the dense fascial layers

Infection of the *sublingual space* so-called Ludwig s angina is characterized by brawny induration of the submaxillary region edema of the floor of the mouth and elevation of the tongue There is severe pain dysphagia and within hours dyspnea from respiratory obstruction The usual causative organism is the streptococcus Mortality was formerly about 50 per cent *Treatment* consists of large doses of penicillin and careful observation If there is significant progression of obstruction during the 4 to 6 hr after treatment is instituted wide incision is indicated for relief of pressure rarely is there extensive suppuration

The retropharyngeal space lies between the muscles anterior to the cervical vertebrae and the pharyngeal mucosa *Retropharyngeal abscess* formerly common in children is manifested by

Specific diseases characterized by suppurative regional lymphadenitis include lymphogranuloma venereum (p 1096) cat scratch disease (p 1098) tularemia (p 905) and bubonic plague (p 907)

Infections of the Hand

These are almost invariably secondary to trauma and are very common Because of the rapidity with which infection can spread through the complex fascial spaces of the hand wrist and forearm with the production of irreparable functional damage *any deep infection in this area should receive expert surgical attention immediately* The importance of this has in no way been lessened by the availability of antibiotics

The ordinary *paronychia* or "run around" is a superficial infection of the epithelium lateral to a nail usually a result of tearing a "hangnail" and most frequently caused by the staphylococcus Hot applications will lead to subsidence of paronychial cellulitis but often a superficial blister of pus appears or the infection burrows beneath the nail to form a painful *subungual abscess* Incision and drainage with partial or complete removal of the nail are then necessary Recurrence is common especially in nail biters and this seemingly trivial infection can cause painful disability Chronic paronychial inflammation produced by various fungi occurs in diabetics and a similar lesion is seen in psoriasis and some types of pemphigus

What appears to be a small furuncle of the webs of the fingers sometimes produces a *collar button abscess* consisting of a superficial and a deep compartment connected by a narrow tract evacuation of the shallow pocket without emptying the deeper abscess can lead to puzzling persistence of infection

Infection of the distal phalanx of a finger usually acquired by pinprick thorn prick etc can lead to the formation of a *felon* or *whitlow* This is a suppurative infection in the tightly enclosed fibrous compartments of the finger pulp (the anterior closed space) which can soon compromise the distal blood supply by compression of the digital arteries with consequent necrosis of bone and the development of osteomyelitis The manifestations are swelling extreme pain and tenderness of the *palmar surface of the fingertip The treatment is* immediate incision using a lateral approach and cutting all the fibrous septa that radiate from the periosteum to the subcutaneous fascia

Suppurative tenosynovitis usually a complication of a puncture wound is an even more serious infection of the hand from the point of view of functional damage early diagnosis and treatment are mandatory to prevent permanent disability from destruction of the tendon or its sheath The three cardinal manifestations of tenosynovitis listed by Kanavel the father of modern surgery of the hand are (1) exquisite tenderness limited to the course *of the sheath (2) the fingers held in flexion (3)* extension of the involved finger producing excruciating pain most marked at the base of the digit *Immediate incision* of the sheath is indicated not only to prevent damage to the tendon itself but to avoid proximal extension of the process into the major fascial spaces of the hand or forearm Vigorous *antibiotic treatment should accompany the* surgery

The definitive treatment of any serious infection of the hand is a matter for a skilled surgeon but the early recognition of the need for surgery often falls to the physician One last infection of the hand that is very important is that complicating *human bites* Neglected injuries of this type almost invariably produce a highly destructive necrotizing lesion the result of infection by a mixture of aerobic and anaerobic organisms A deliberately inflicted bite on the hand or elsewhere is usually recognized as dangerously contaminated but wounds on the knuckles produced by striking an opponent s teeth with the fists may not be recognized as potentially dangerous *In general bite wounds should be* cleaned thoroughly and *not* sutured patients should be given prophylaxis for tetanus and antibiotics preferably penicillin and streptomycin and observed carefully

Chronic Cutaneous Ulcers

A partial list of the causes of chronic ulcers of the skin includes circulatory disturbances such as varicose veins and obliterative arterial disease extensive injury from frost bite or burns trophic changes accompanying many neurologic disorders bedsores or decubiti systemic diseases such as sicklemia and myxedema neoplasms and several infections of mycotic and spirochetal origin No matter what the underlying disease responsible for the lesion secondary infection is very likely to occur and to interfere with healing complicate grafting or other restorative procedures or produce extension of the process

The management of secondary bacterial infection in skin ulcers associated with obliterative arterial *disease a common problem in diabetics* is especially important because infection is frequently the factor that precipitates spreading gangrene and makes amputation necessary

Studies of the microflora of chronic cutaneous ulcers have almost invariably shown bacteria of many species including *staphylococci* aerobic and anaerobic streptococci coliform bacilli and members *of the Proteus and Pseudomonas* groups Depending upon the patient s environment and upon

many surgeons prefer to explore the area by needle aspiration before operation

Retroperitoneal Infections

Strictly speaking all perinephric and many subphrenic abscesses are located outside the peritoneum but the term *retroperitoneal abscess* usually refers to infection in the lumbar and iliac regions Suppuration in these areas is relatively rare but the importance of recognizing its existence in patients with fever and low back pain in terms of instituting surgical drainage is great In the review of retroperitoneal infections published by Neuhof and Arnheim listed in the references at the end of this chapter the average duration of illness in 65 patients before diagnosis was approximately 1 month

Infection in the retroperitoneal spaces appears to arise rather frequently as a complication of bacteremia particularly in staphylococcal disease Other sources are extension from posterior perforations of the appendix or colon renal or spinal infections and suppurative lymphadenitis in the iliac area usually secondary to streptococcal infections of the lower extremity in children

In *lumbar abscess* there is tenderness and spasm of the back muscles on the affected side and a mass is usually palpable in the lumbar region or in the abdomen There may be a prominent tender abdominal mass without lumbar pain or spasm Flexion of the hip (psoas sign) occurs in a few cases but is more often present with infections lower in the retroperitoneal area *Fever leukocytosis* and *lumbar spasm* should suggest the diagnosis The absence of a palpable mass can lead to protracted observation and it is in these instances that palpation under anesthesia is often helpful

In *iliac abscess* there is abdominal pain in the iliac or inguinal region and particularly when the psoas muscle is involved there may be severe pain referred to the hip thigh or knee Careful palpation of the lower abdomen usually reveals a mass and fullness and tenderness on rectal examination are common Hip spasm (psoas sign) is often present

X ray may delineate the inflammatory mass pyelography shows displacement of the kidney in some cases of lumbar infection scoliosis with concavity on the side of the infection and blurring of the psoas shadow are also useful findings

Treatment consists of surgical drainage and appropriate antibiotic therapy

Renal Abscess

Single or multiple abscesses of the renal cortex are almost invariably the result of metastatic implantation of staphylococci from another focus It is believed by many that the infection is initiated in glomeruli There is no relationship to previous renal disease the infection occurs in younger individuals is usually unilateral and occurs on the right side oftener than the left Many patients give a history of recent superficial infection such as furuncle The onset is abrupt with chill and fever followed by costovertebral pain and tenderness of moderate severity The urine contains *no white cells* usually a few red cells and a trace of albumin Stained urinary sediment will show myriads of gram positive cocci and this finding is diagnostic Transient gross hematuria can occur at the onset The white blood count is usually elevated and may exceed 30 000 per cu mm Physical signs are usually localized to the region of the kidney but abdominal spasm can lead to confusion with appendicitis or cholecystitis Early in the disease ureteral calculus or acute hydronephrosis may be considered as possible diagnoses Sudden onset of fever leukocytosis and renal pain in the absence of pyuria suggest the diagnosis especially in a patient with infection elsewhere *Treatment* consists of appropriate antibiotics adequate fluids and relief of pain An abscess may suddenly discharge into the renal pelvis with relief of pain and the passage of cloudy urine containing enormous numbers of leukocytes and bacteria *Complications* include formation of a thick walled chronic renal carbuncle" requiring surgical removal rupture into the perirenal space and secondary pyelonephritis usually produced by coliform bacilli Recovery is ordinarily prompt and chronic sequelae are rare

Perinephric abscess is virtually always secondary to infection elsewhere in the body usually superficial staphylococcal or streptococcal infection The perirenal tissue may be seeded directly in the course of bacteremia by rupture of a renal cortical abscess into the perinephric space or by chronic pyelonephritis particularly when renal calculus or pyonephrosis is present Flank pain with radiation to the upper abdomen or even the shoulder nausea vomiting fever leukocytosis tenderness with spasm of flank and upper abdominal muscles and a palpable mass which moves with respiration are the main manifestations Except where there is preexisting pyelonephritis perinephric abscess is *not* accompanied by urinary symptoms In a few patients elevation of the diaphragm on the diseased side occurs and leads to confusion with subphrenic infection The psoas muscle is involved by the inflammatory process and patients are frequently more comfortable with the thigh held in flexion X ray occasionally will reveal a mass there is usually blurring of the kidney silhouette and the psoas shadow is indistinct on the involved side *Treatment* by surgical drainage and systemic administration of antibiotics (*not* urinary antiseptics) is usually followed by dramatic subsidence of pain and fever

dysphagia progressive stridor pain and fever The bulging mass is easily seen and can completely occlude the airway within hours Incision and drainage are mandatory spontaneous rupture can lead to death by aspiration Tuberculous abscess secondary to spinal disease occasionally presents in the retropharyngeal space it is painless and relief of obstruction follows surgical incision The pharyngomaxillary and submastoid spaces lie high and lateral in the neck the latter slightly posteriorly *Suppuration in the submastoid space a Bezold abscess* is usually secondary to otitis and produces nuchal rigidity which may lead to a mistaken diagnosis of otogenous meningitis Infection can extend down the carotid sheath to the mediastinum A suppurative thrombophlebitis of the jugular vein usually accompanies this type of spread and the vessel is easily felt as a tender cord Bacteremia and systemic spread of infection makes this a dangerous complication there are many who advocate excision of the involved venous segment Spontaneous rupture of the carotid artery and rapid death from exsanguination is a rare complication of infections of this type

Splenic Abscess

The majority of splenic abscesses are produced by hematogenous dissemination of infection from a focus in the skin endocardium or elsewhere Trauma to the spleen with formation of a sub capsular hematoma or bland infarction of the organ can lead to infection in the course of transient bacteremia Occasionally extension of a nearby infection (usually left subphrenic abscess) or perforation of the colon or stomach into the spleen is the source Onset is sudden with chills fever and left upper quadrant pain There is tenderness and muscle spasm and the skin and subcutaneous tissues overlying the spleen may be edematous In volvement of the upper pole commonly leads to left pleuritic pain radiating to the shoulder with elevation of the diaphragm or left pleural effusion Lower pole abscess gives signs of peritoneal inflam mation The spleen is usually palpable and tender a friction rub is often audible Disorders to be considered in differential diagnosis are subphrenic *abscess infection of the left lung bland infarction* of the spleen pancreatic pseudocyst and abscess secondary to perforation of the transverse colon *Treatment* consists of antibiotics and splenotomy or if the organ is easily mobilized splenectomy If the abscess is a complication of generalized pyogenic infection immediate surgery may be contraindicated Splenic infarction in subacute bac terial endocarditis caused by *Streptococcus viridans* almost never suppurates but in endocarditis in fected splenic infarcts are a rare cause of continued bacteremia in the face of massive chemotherapy and splenectomy may then be the treatment neces sary *to achieve the final eradication of the* or ganism

Subphrenic Abscess

Peritoneal infections show a striking tendency to localize in the upper part of the abdomen between the transverse colon and the diaphragm In a few instances suppuration in this area seems to be hematogenous in origin but the vast majority of subphrenic abscesses are the result of extension from perforations of the gastrointestinal tract or from biliary tract infections The most frequent sources of infection are appendicitis perforations of the stomach and duodenum and ascending cholangitis *Any patient with persistent fever and a history of recent intraabdominal sepsis should be suspected of having a subphrenic abscess* In considerably more than half of the cases the patient has undergone recent laparotomy The avenues by which infection reaches the subphrenic region are the same as those described for hepatic abscess (p 1518) and appendical abscess (p 1455) Sub phrenic abscess is at least five times more frequent on the right side

The *manifestations* include fever upper quadrant pain and tenderness The localizing signs are by no means striking in all cases however It is becom ing evident that the widespread practice of "cover ing postoperative patients with antibiotics prophy lactically can attenuate subphrenic infection with out eradicating it and that the result may be an insidiously progressive illness with weight loss and low grade fever beginning weeks or months after a laparotomy Faxon has emphasized the fol lowing findings in the diagnosis of subphrenic in fection point tenderness over the lower ribs tenderness of the area when the lower rib cage is compressed or percussed elevation and fixation of the diaphragm confirmed by x ray other signs of diaphragmatic pleurisy such as pain referred to the shoulder hiccoughs or pleural effusion X rays will show an air fluid level beneath the diaphragm eventually in about one fourth of the cases but this finding is less frequent in early abscess The gas is usually from a perforated viscus or enters *through an external sinus* and is only rarely the result of bacterial multiplication

In the presence of frank suppuration the treat ment is surgical drainage Actually there are several subphrenic spaces anterior and posterior and the exact incision *employed is dependent upon the* compartment involved Often subphrenic infection becomes evident before suppuration ensues and such cases of *subphrenic cellulitis* often subside without drainage antibiotics alone being sufficient to control the process *It is important to avoid in* cision of an area of subdiaphragmatic cellulitis and

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144 INFECTIONS OF THE URINARY TRACT (Including Pyelonephritis)

Paul B Beeson

Bacterial infections of the urinary tract constitute one of the major medical problems encompassing all fields of practice They may present themselves as primary acute infectious diseases as complications of other disorders or as chronic symptomless processes chiefly dangerous because of the threat of gradual destruction of the kidney They are notoriously resistant to treatment and prone to relapse and recurrence

Etiology Many different microorganisms may infect the tissues and fluids of the urinary organs but by far the commonest are the coli aerogenes group of gram negative bacilli Other microorganisms which may be found include enterococcus Proteus Pseudomonas Chromobacteria staphylococcus and certain yeasts Infection by other than the coli aerogenes organisms is generally related to previous instrumentation of the urinary tract with or without the use of chemotherapeutic agents *Proteus* and *Pseudomonas* urinary infections for example are virtually never seen except in patients who have had catheters or other instruments passed through the urethra The relative importance of staphylococcal infections has probably been exaggerated in the past because of the prevalent custom of culturing urine only in a liquid medium a procedure which negates any possibility of estimating the numbers of bacteria present in a given quantity of urine Since staphylococci are commonly present in the urethra they may therefore be recovered in such cultures The employment of quantitative bacteriologic techniques reveals that staphylococci play a minor role in the total problem of urinary tract infection

Pathogenesis *Sources of Infection* The entire urinary tract should be looked upon as an anatomic unit in which infection of one part can easily spread to another While it is probable that the source of infecting bacteria is the intestinal tract there is considerable disagreement regarding the routes by which microorganisms usually get from there to the urinary tract One view holds it to be by way of the circulating blood another favors the concept that bacteria gain entry by way of the urethra and pass upward to the kidneys through the bladder and ureters The latter seems especially plausible as an explanation of the far greater frequency of spontaneously occurring infections in females since the short urethra and its nearness to the anus should provide more opportunity for fecal bacteria to reach the bladder cavity A third hypothesis that lymphatic connections between the bowel and the urinary tract or between the lower and upper urinary tracts are important avenues for spread of infection has little to support it On the basis of clinical correlations there is much evidence favoring the view that the ascending route i e lower to upper urinary tract via the urinary passages is the most important one The possibility remains however that bacteria occasionally are carried to the kidney by way of the blood stream thus inciting an infection which later spreads downward along the course of urinary flow

Associated Conditions AGE AND SEX Precise estimates cannot be given but it can be said with assurance that urinary tract infections are far more frequent in females than in males except in older age groups where prostatic obstruction accounts for a high incidence in males There is also a high incidence in children between the age of six months and two years especially females this is thought to be related to fecal soiling of the urethral meatus during the diaper period

PREGNANCY Acute pyelonephritis occurs in about 2 per cent of pregnant women usually after the fourth month at a time when some dilatation of the ureters and kidney pelves occurs physiologically Urinary tract infection can be demonstrated in about 20 per cent of patients with toxemia of pregnancy

DIABETES MELLITUS Urinary tract infection is three or four times as common in diabetics as in other persons of comparable age Factors which may contribute to this include the supposed increased susceptibility to infection in diabetics the enhanced growth of bacteria in sugar-containing urine and more frequent catheterization About half of all reported cases of the fulminating form of pyelonephritis called *necrotizing papillitis* have been in patients with diabetes

OBSTRUCTIVE UROPATHY Any impediment to the free flow of urine—tumor stricture or stone—results in hydronephrosis and a greatly increased frequency of urinary tract infection Autopsy statis

and unless intrinsic renal disease is present recovery is complete

Rectal Abscess

Suppurations of the anorectal region have been classified anatomically in several ways most of the classifications being based upon the surgical approaches required for drainage Infection in the apocrine glands (hidradenitis) or folliculitis in the perianal region extension of cryptitis or obstructions in the anal glands which open into the crypts of Morgagni and contamination of submucosal hematomas sclerosed hemorrhoids or anal fissures can lead to abscess formation These are *usually painful easily palpable often visible* on inspection and yield readily to hot applications and drainage

Difficulties in diagnosis are more likely to arise with infections higher in the rectum especially those above the pelvic diaphragm the types that Gaston and Warren have called *supralevator abscess* Patients with this type of infection often have fever malaise and leukocytosis for several days or even weeks before any symptoms referable to the rectum develop There is vague pelvic discomfort relieved by defecation and constipation punctuated by short episodes of diarrhea is common In males the inflammation often involves the base of the bladder and urinary urgency and finally retention is not infrequent This of course centers attention upon the urinary tract as a source of fever and malaise Eventually the abscess becomes known by severe pain chills and fever and palpation and instrumentation will reveal the swelling in the rectal ampulla Such an abscess can surround the rectum and produce narrowing that is differentiated from that caused by neoplasm by the fact that the mucosa remains intact A useful sign of deep rectal abscess is the eliciting of severe pain by pressure in the region between the anus and the coccyx The supralevator space is continuous with the ischiorectal space with both the gluteal and obturator regions and with the retroperitoneal space In neglected cases the abscess may drain through the skin of the perineum the groin or the buttock or may extend as high as the perirenal areas Rectal abscesses are not uncommon in patients with diabetes and infections in this area are also peculiarly frequent in patients with monocytic leukemia Because the clinical picture may be that of fever of unknown origin for a long period it is important that thorough digital and endoscopic examination of the rectum be carried out in febrile patients A rectal examination should be made in all patients with diabetes especially if ketosis is present failure to observe this rule has more than once led to delay in detecting the infection responsible for diabetic ketosis or coma

Treatment consists of incision and drainage hot sitz baths analgesics and penicillin and streptomycin or other antibiotics as indicated by culture of the exudate

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cystitis are usually associated and either one may precede the other

On physical examination in addition to fever and some generalized tenderness of the muscles the key finding is tenderness on deep pressure in one or both costovertebral areas or on bimanual palpation of the kidney region Occasionally even this sign is absent in acute pyelonephritis

Except in individuals with ureteral obstruction as by stone the manifestations of acute pyelonephritis usually subside within a few days even without specific antibacterial therapy the patient becoming symptom free although laboratory tests may show that bacteriuria and pyuria are still present It would seem therefore that after the first acute inflammation in the renal parenchyma with swelling and perhaps intermittent plugging of the ureter by inspissated pus to account for the pain there ensues a change in character of the disease with the parenchymal infection going over to a more indolent process involving many small foci in the kidney substance but with continuing growth of bacteria in the kidney pelvis and the descending urinary passages

Undoubtedly some individuals recover completely and permanently after an attack of acute pyelonephritis but in a considerable proportion of cases there are repeated attacks at irregular intervals sometimes over a period of many years between these the patient is symptom free It is possible however that bacilluria and pyuria could be demonstrated during these free intervals if looked for repeatedly The important point to be stressed is that infection in any part of the urinary tract is capable of subclinical continuation which may persist for months or years and which in the kidney eventually may cause serious destruction of essential tissue Such a patient may exhibit no symptoms and may live an apparently normal life for long periods even though urine examination gives continuing evidence of active infection This is the feature which makes it so treacherous and such an important cause of serious renal disease

In the *chronic progressive form of pyelonephritis* there are no distinctive manifestations until one of the serious complications makes its appearance i e renal failure or hypertension Before this time there may be some lassitude lack of energy and mild normochromic anemia Occasionally patients with long standing pyelonephritis are found to have large spleens the pathogenesis of which is obscure

Laboratory Findings In acute pyelonephritis there is a polymorphonuclear leukocytosis in cystitis and in chronic urinary tract infection the white blood cell picture is normal The urine sediment in acute pyelonephritis or cystitis usually reveals numerous leukocytes occurring singly in clumps and in casts and occasionally some red blood cells Bacteria can easily be demonstrated by suitable stains In chronic infections of low grade activity diagnosis may be very difficult on the basis of urine sediment There may be a few pus cells or they may be found only intermittently during repeated urinalyses Special stains for the so-called "glitter cell are thought by some to be of value in pointing to the presence of chronic pyelonephritis although the demonstration of this cell cannot be regarded as diagnostic

Culture of the urine is the most important diagnostic procedure In acute pyelonephritis bacteria are nearly always demonstrable in large numbers sometimes hundreds of millions of them per milliliter In subacute and chronic infections bacteria may appear in the urine intermittently and in relatively small numbers Consequently inasmuch as urine cultures may be contaminated by small numbers of bacteria lying in the urethral canal even in a specimen obtained by catheter it is important that the laboratory employ some quantitative method for determining the number of organisms present in the urine and that the urine be cultured on a solid medium in order to estimate the relative preponderance when mixed growth is obtained A rough quantitative estimate of the situation can be made by means of a Gram stain on uncentrifuged freshly voided urine If bacteria can be found by this method it can be assumed that the number present is greater than would be expected to occur as a result of urethral contamination If quantitative cultures reveal more than 10 000 bacteria per milliliter of freshly passed urine it can be assumed that active infection is present If less than 1 000 they are likely to be of no significance Between these two figures one cannot draw a positive conclusion *Intravenous pyelogram* may be of value in the diagnosis of pyelonephritis evidenced by an asymmetry between the kidneys as judged by their size and the density of the renal shadows This of course is a reflection of the patchy distribution of the pyelonephritis lesion It is said also that careful radiographic studies will show hypotony of the calyces pelvis and ureters in a high proportion of these cases *Biopsy of the kidney* by needle may be the only means of demonstrating low grade pyelonephritis but its value is also limited by the spotty distribution of the lesions However culture of the biopsy needle occasionally yields bacteria even when the histology is inconclusive

Treatment The soundest approach to treatment is based upon a conception of the urinary tract as a complex system wherein infection introduced into or persisting in any one part may spread to all the others For example certain drugs which have been recommended for treatment of urinary tract infection appear to be capable of acting only in urine These which include mandelic acid Urotropin

tics indicate that pyelonephritis occurs about a dozen times more often when there is hydronephrosis than when the kidneys show no sign of increased hydrostatic pressure

INSTRUMENTATION There can be no question that infection of the lower urinary passages is sometimes initiated by bacteria carried on catheters or other instruments being passed through the urethra into the bladder

METABOLIC DISORDERS There appears to be an unusually high incidence of urinary tract infection in patients with nephrocalcinosis and in those with chronic hypopotassemia The relation of the latter is obscure in nephrocalcinosis the important factor may be production of tubular obstruction by the deposits

NEUROGENIC BLADDER DYSFUNCTION Interference with the nerve supply to the bladder as in spinal cord injury tabes dorsalis multiple sclerosis etc is likely to be associated with urinary tract infection The infection may be initiated by the use of catheters for bladder drainage and favored by the prolonged standing of urine in the bladder Additional factors which often operate in these patients are bone demineralization due to immobilization hypercalcuria calculus formation and obstructive uropathy

Urinary tract infections can be produced in experimental animals by several methods including inoculation of bacteria into the pelvis or substance of the kidney or into the bladder urine Certain organisms such as staphylococci and Monilia are capable of causing infection in the normal kidney when they are injected by the intravenous route Coliform organisms will not do this unless the kidney has previously been injured as by mechanical bruising or acute obstruction of the ureter It has also been shown that the renal scarring resulting from a staphylococcal infection can render the kidney susceptible to infection by colon bacilli injected intravenously

The frequent association of urinary tract infection with an obstructive lesion has led to the widespread view that stasis of urinary flow is a prime factor in the development of infection In support of this is the fact that urine is a good medium for growth of bacteria hence prolonged opportunity for multiplication during slow passage along the tract would provide a heavier inoculum to which the kidneys and other tissues of the tract are exposed This concept is the basis for the custom of forcing fluids in treating urinary infections There may be an additional factor to explain the association between obstruction and urinary infection the effect of increased hydrostatic pressure One can cite several examples where clinical experience demonstrates that blockage to an excretory duct seems *to render an organ more susceptible to the* development of pyogenic infection For instance bacterial cholangitis is seldom encountered except when there is obstruction to the biliary passages It seems unlikely that the mere flushing out of bacteria in the excretory fluid could be the sole *factor of protection against these infections* To assess the relative importance of stasis and increased pressure is difficult since slowing of flow of the fluid is an inevitable accompaniment of obstruction and dilatation of the passages above the level of obstruction It can be said with assurance that even when a profuse diuresis is obtained in a patient with partially obstructed urinary tract this seldom achieves cure of an infection whereas relief of the obstruction with or without diuresis frequently is followed by subsidence of infection

In urinary tract infection two different infected areas are interacting the tissues and the urine itself On the basis of animal experiments and clinical observations it seems clear that infection beginning in one can spread to the other The complexity and extent of the urinary system may be responsible then for the tenacity of infection in it One conceives of chronic pyelonephritis as an indolent process consisting of many isolated microabscesses some of them within single tubules Here bacterial growth may be slow phagocytosis inefficient and antibacterial drugs may not be capable of exerting optimal effect Yet such areas may from time to time discharge their contents into the urinary passages affording opportunity for rapid bacterial multiplication and spread to other parts of the system In the urine phagocytosis is probably even less effective than it is in tissues and elimination of bacteria may call for more than simple bacteriostasis This line of reasoning leads to the conclusion that optimal results in drug treatment require the use of an agent or a combination of agents capable of killing the infecting bacteria both in the tissues and in the urine

Manifestations *Cystitis* is accompanied by pathognomonic local symptoms frequency and urgency of micturition and burning pain *felt in the* urethra during and immediately following the act Cystitis alone almost never gives rise to prominent systemic manifestations of infection such as fever above 101 F muscular pain nausea vomiting and prostration and when present these should cause the physician to suspect concomitant infection in the kidney prostate or some other part of the body

The symptoms of *acute pyelonephritis* generally develop rapidly over a period of a few hours or a day or two The characteristics are aching pain in one or both lumbar regions and fever which may be high (103 to 105 F) often with one or more shaking chills There may be nausea vomiting and diarrhea or occasionally constipation Symptoms of

SUBACUTE BACTERIAL ENDOCARDITIS DUE TO VIRIDANS STREPTOCOCCI

Definition This is a prolonged febrile often fatal disease resulting from streptococcal infection of a heart valve characterized by fever heart murmur splenomegaly embolic phenomena and bacteremia

Etiology The viridans group of streptococci includes several different varieties (p 868) Those which are important causes of subacute bacterial endocarditis are *Streptococcus salivarius* *S mitis* and *S bovis* normally present in the mouth the enterococcus *S fecalis* normally present in the intestinal tract and *S sanguis* which has been encountered mainly in cases of bacterial endocarditis

Pathogenesis In the great majority of cases bacterial infection is established on a valve which has been previously damaged by rheumatic fever Changes caused by congenital heart disease or rarely by arteriosclerosis or syphilis may also provide the foundation for this infection The mitral valve is the one most often involved the aortic is second in frequency The valves on the right side are affected far less often i e in only about 15 per cent of cases including those in which the mitral and aortic are also involved This corresponds with the frequency of involvement of the four valves in rheumatic heart disease Valves only slightly damaged appear to be more frequently affected than those which are extensively scarred This is partly attributable to the fact that people live longer with slightly damaged than with severely damaged valves and hence have more opportunity to contract the infection but other factors which may play a part include turbulence of blood flow over the valve the circulation within the valve and the amount of scar tissue present It is generally agreed that bacterial endocarditis rarely occurs in persons with chronic auricular fibrillation

A similar process may become established on a patent ductus arteriosus at the site of coarctation of the aorta or in an arteriovenous fistula. These infections are called subacute bacterial *endarteritis*

Bacteria must reach the heart valves by way of the blood stream There is abundant evidence to show that entry of bacteria into the circulation is not infrequent For example it is a common occurrence in minor surgical procedures such as tooth extraction and tonsillectomy Bacteremia can occur in persons with periapical dental infection simply as a result of grinding the teeth together Ordinarily such brief episodes of bacteremia are not serious because the organisms are quickly phagocytized by the reticuloendothelial system If however living bacteria happen to lodge in or on a damaged heart valve the stage has been set for the establishment of a grave infection The manner in which a colony of bacteria becomes established in such a location is not known with certainty The fact that preexisting deformity of the valve is usually a requirement brings up the possibility that roughening of the endocardial surface or some change in blood supply to a valve may predispose to implantation of the infection Possibly the bacteria become lodged beneath small platelet thrombi on the surface of a valve Possibly they are carried into a valve through its blood supply and are deposited beneath the endocardium In any event the primary site of bacterial growth is usually near the free edge of the valve at the line of closure and on the outflow surface This growth stimulates the deposition of platelets and fibrin and leads to the formation of a *vegetation* This structure increases in size and may extend onto the adjacent mural endocardium Meanwhile the valve leaflet is undergoing gradual necrosis Granulation tissue grows into the vegetation from the valve but capillaries seldom reach the periphery of the infected necrotic area Nests of growing bacteria are scattered through the vegetation those which are in the avascular outer portion of the vegetation are protected from phagocytosis since leukocytes do not seem able to penetrate the area This protection from phagocytosis may be the principal factor which permits survival of bacteria and persistence of the infection and which accounts for the unsatisfactory therapeutic results obtained with drugs which are only bacteriostatic

Organisms are constantly shed into the blood from the vegetation but their stay in the circulation is very short, since studies have shown that one-half to one-third of the organisms entering the arterial blood are removed during each circuit of the body The principal sites of removal are organs rich in reticuloendothelial elements—i.e liver spleen, and bone marrow

Vegetations of bacterial endocarditis are friable and fragments are occasionally broken off by motion and the current of blood passing over them These particles are carried in the blood to all parts of the body where they eventually lodge as emboli The damage produced by an embolus depends principally on its size and the vessel which happens to receive it Emboli which lodge in the brain in the mesentery or in arteries of the extremities are most likely to have serious effects Those carried into the walls of large arteries by vasa vasorum can cause mycotic aneurysms which may rupture at a later time

It should be noted that the infected emboli and the free bacteria which are constantly disseminated throughout the body very seldom create metastatic abscesses The infecting organisms are usually of

and nitrofurantoin (Furadantin) often suppress but do not eradicate infection The antibiotics are generally also effective in tissues although some are more likely to exert a bactericidal action than others Sulfonamides are principally bacteriostatic Another essential principle in management is to consider what factors in the patient may be contributing to the infection such as obstruction faulty bladder innervation diabetes etc these were mentioned in a preceding section Relief of obstruction or correct management of diabetes may be the essential factor in eradicating the infection Although no further space will be devoted to this aspect of treatment its importance cannot be overemphasized

In antibacterial therapy best results are obtained when there is individualization of the treatment Advertisements and medical articles which describe the effectiveness of any one agent in the treatment of urinary infections are misleading There is a wide choice of agents which may be used and the best results are obtained by employing the therapy suited to the microbes operating in the individual patient

In view of the varying conditions under which bacteria grow in urine and in urinary tract tissues it seems probable that the ideal chemotherapeutic attack is to employ a form of treatment which is capable of bactericidal not simply bacteriostatic action Determination of possible synergistic or antagonistic effects of combinations of agents on the bacteria to be attacked is sometimes necessary Streptomycin is perhaps the most valuable of all agents available its main defect being the rapidity with which bacteria develop resistance to it this defect can be lessened however by giving streptomycin in combination with another antibiotic such as tetracycline Enterococcus infections may yield to a combination of penicillin and streptomycin For *Proteus* infections the antibiotics most likely to be beneficial are penicillin in massive doses or neomycin For *Pseudomonas* infection polymyxin may be required Since the use contraindications dosages etc of these agents are covered in detail in another chapter (p 814) they will not be repeated here

In view of the nature of urinary tract infection it seems possible that prolonged treatment for from 2 weeks to several months might be ideal This however is impractical in many situations Nevertheless every effort should be made to administer the appropriate drug or drugs for 7 to 10 days no matter how prompt the symptomatic response may be It is essential to obtain follow up urine cultures 1 to 3 months after discontinuing of treatment to avoid overlooking smoldering asymptomatic infection with its potentialities for eventual development of serious disease It is probably unwise to employ catheter specimens for these follow up examinations since they may actually cause reinfection of the urinary tract and are not wholly reliable as methods of obtaining uncontaminated urine from the bladder With proper care it is possible to obtain suitable *clean voided specimens of urine from* females as well as males

Prognosis It is usually possible to obtain a dramatic cessation of symptoms in the treatment *of acute urinary tract infection not complicated by* other diseases The dangerous feature is the possible persistence of chronic asymptomatic infection which will gradually destroy the kidney or lead to development of hypertension (p 1319) It is not possible to state what the risk is that a simple cystitis may spread to one or both kidneys and it is often extremely difficult to decide whether infection is limited to the lower urinary tract Nevertheless the fact that a significant proportion of patients coming to autopsy show evidence of pyelonephritis and some degree of renal damage indicates the great importance of this problem In patients with some of the complicating diseases mentioned above particularly neurogenic bladder irremediable obstruction or multiple stones *eradication of urinary tract infection is exceedingly* difficult if not impossible Even here however it is usually possible to minimize the extent of the process by means of comprehensive care including surgical measures prevention of stone formation and appropriate chemotherapy guided by reliable laboratory procedures

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145 BACTERIAL ENDOCARDITIS

Paul B Beeson

Bacterial endocarditis includes a variety of clinical syndromes some of which pursue a rapid and acute course whereas others evolve slowly over a period of many months By far the commonest type of bacterial endocarditis is the subacute variety caused by streptococci of the *viridans* group

liver When present these manifestations may dominate the clinical picture and may in fact obscure the diagnosis

The *manifestations of embolic phenomena* depend upon the tissues involved There may be hemiplegia meningeal inflammation infarction of lung myocardium mesentery spleen or kidney or occlusion of peripheral arteries In right sided endocarditis or patent ductus endarteritis emboli are carried to the lungs these may be responsible for an erroneous diagnosis of pneumonia

The *course* of subacute bacterial endocarditis is variable and may last from 1 month to 2 years Before effective methods of treatment were available the majority of patients died within 9 months of the onset

Intercurrent infections are not very common although bronchopneumonia occurs occasionally In rheumatic subjects the development of arthritis produces a clinical picture which may be indistinguishable from acute rheumatic fever

Since the introduction of penicillin therapy which controls the infection in most instances the principal *cause of death* in subacute bacterial endocarditis is progressive intractable cardiac decompensation This is probably the result of valvular damage which renders the heart mechanically less efficient together with myocarditis and increased demand for cardiac work occasioned by fever and anemia Some patients die following cerebral myocardial or mesenteric embolism while others succumb to a progressive "toxemia" of infection without localizing manifestations Rarely death is due to uremia caused by a progression of the nephritis this is more likely to occur in the relatively inactive cases Sometimes coma and death are the result of multiple small cerebral emboli which do not give localizing signs

Laboratory Findings The *leukocyte count* in the peripheral blood is usually moderately elevated but may be within the normal range *Circulating macrophages* may be found in smears of the peripheral blood These are thought by some hematologists to be of diagnostic value In cases of long standing a moderately severe normochromic *anemia* may be present There may be an *increase in serum globulin* and *cold precipitable globulins* are found in some cases The erythrocyte *sedimentation rate* is elevated Microscopic hematuria is very common and is helpful in diagnosis Albumin may also be found in the urine The *blood culture* is positive for *Streptococcus viridans* in about 80 per cent of cases In these cases the number of colonies of bacteria per milliliter of blood is usually approximately the same from day to day In a minority of instances the blood culture is consistently negative for reasons which are not clear It may be that in these cases the bacteria grow more deeply in the vegetations and hence do not have free access to the circulating blood It is often said that bacterial endocarditis located on the right side of the heart is more likely to be associated with negative blood cultures but there is little foundation for this assertion Actually it is not at all uncommon for bacteremia to be present in cases of right sided bacterial endocarditis

Differential Diagnosis The diagnosis of subacute bacterial endocarditis may be very easy or may be extremely difficult depending on the prominence of the various manifestations In a patient with the cardinal manifestations of fever heart murmur splenomegaly petechiae and clubbing of the fingers the diagnosis is obvious On the other hand subacute bacterial endocarditis can be a most difficult diagnostic problem since it can simulate a variety of diseases *The possibility of subacute bacterial endocarditis should be considered in every patient with fever and heart murmur* The diagnosis is missed most often in elderly patients especially those whose presenting complaint is the result of a cerebral embolic accident in such individuals a diagnosis of cerebral thrombosis or hemorrhage is likely to be made and little consideration given to the presence of a systolic murmur or low grade fever Heart murmur is so constantly present in the established disease (99 2 per cent of Kelson and White s series of 250 cases) that the diagnosis of subacute bacterial endocarditis can be excluded fairly safely in patients without murmurs An exception to this is the not infrequent absence of a murmur in early infections of the aortic valve in such cases a typical murmur may appear during treatment

This disease is one of the classic causes of "fever of undetermined origin" the important differential diagnostic points of which are covered elsewhere (p 72) Chief among the disorders which can be confused with it are systemic lupus erythematosus Hodgkin s disease miliary tuberculosis brucellosis periarteritis nodosa and acute rheumatic fever

Prognosis The natural course of the disease almost invariably leads to death the incidence of spontaneous recovery being less than 1 per cent In the past many forms of therapy were tried but found ineffective these included transfusions from immunized donors autogenous vaccines antiseptic drugs irradiation of the heart valves and so on With sulfonamide therapy a small proportion of patients probably not more than 4 per cent of those treated recovered The advent of antibiotic treatment brought about a great change in outlook and at present about 70 per cent of these *infections can* be brought under control Factors which point to

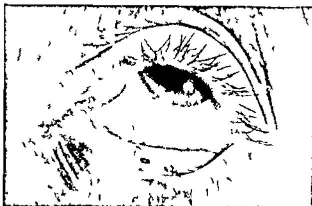


Fig 141 White centered conjunctival petechia in a patient with subacute bacterial endocarditis (*Courtesy Dr John Wedgwood Cambridge England*)

low pathogenicity and when separated from the protection of the vegetation they are readily de stroyed An exception should be made for cases in which enterococcus is the infecting organism since they may develop suppuration at sites of embolization especially in the spleen

The *myocardium* may be the site of a low grade inflammatory process which is probably an em bolic myocarditis The *spleen* is nearly always en larged and in most instances shows areas of in farction The *kidneys* which because of their rich blood supply constantly receive small emboli show changes of focal embolic nephritis In addition a diffuse glomerulitis is commonly encountered These processes may result in renal insufficiency which can be fatal

Manifestations In about one third of cases symp toms begin 1 to 3 weeks after some other illness such as acute respiratory infection or septic abor tion or some operative procedure such as dental extraction tonsillectomy or urethral instrumenta tion

The symptoms and course of subacute bacterial endocarditis do not conform to any single typical picture since they depend upon many factors in cluding the extent of the preexisting valve damage and the chance distribution of emboli The symp toms of congestive failure may be superimposed at any time during the course of the disease

In only about 25 per cent of cases is the onset of symptoms sufficiently dramatic that it can be recalled with certainty by the patient More often the illness begins very insidiously and the patient cannot name the exact time of onset The principal *symptoms* are weakness malaise feverishness chills (occasionally) sweating weight loss ano rexia nausea joint pains paresthesias and paraly sis

The patient usually appears chronically ill The skin is pale and sometimes has a tan color the so called *café au lait* appearance The skin may be flushed and hot or it may be wet with perspiration Tiny *petechial hemorrhages* may be visible in any part of the body they are particularly evident on mucosal surfaces the conjunctiva the palate or the buccal mucosa Some of the petechiae in the conjunctiva have white or gray centers (see Fig 141) these are considered by many to be of diag nostic significance but are occasionally seen in other conditions A distinctive lesion can sometimes be seen in the ocular fundus—the Roth spot" This consists of a circular or oval pale area surrounded by a ring of hemorrhage usually near the disk (Similar lesions occur in acute myelogenous leu kemia and in septicemia) Petechiae may be found on any area of the skin they have to be distin guished from other lesions such as small angiomas The latter usually blanch when pressed with a glass slide It is sometimes helpful to circle all suspicious lesions with ink and reexamine them later Old petechiae fade in a day or two and new ones appear in other areas whereas angiomas do not change Petechial hemorrhages in the nail beds usually are located near the distal margin and have a linear shape resembling embedded splinters hence the name *splinter hemorrhages* Small pain ful reddish or purplish areas in the pulps of the fingers (*Oslers nodes*) may develop during the course of the disease they usually disappear within a day or two Larger painful erythematous areas may appear from time to time on the palms of the hands or soles of the feet Embolization of small arteries in the digits or in the nose occasionally produces a local area of gangrene In cases of long duration *clubbing of the fingers* is likely to be present Examination of the heart reveals the signs of the preexisting valvular defect Changing mur murs have often been mentioned as helpful in diag nosis but too much stress should not be given this sign The changes which do occur are most often due to the circulatory effect of anemia and fever Occasionally however there are rather striking fluctuations these are especially likely to occur in patent ductus endarteritis The *spleen* is palpable in more than one half of all cases following an in farction there may be severe pain and tenderness in the left upper quadrant and a friction rub may be audible over the left lower costal margin Inflam mation of *joints* occurs in about one fourth of all cases and may simulate acute rheumatic fever The pathogenesis of these arthritides is not clear

Symptoms and signs of congestive heart failure may be present from the onset or may appear at any time during the course of subacute bacterial endocarditis There may be orthopnea distention of the neck veins peripheral edema rales in the lungs pleural effusion and a large tender swollen

liver When present these manifestations may dominate the clinical picture and may in fact obscure the diagnosis

The *manifestations of embolic phenomena* depend upon the tissues involved There may be hemiplegia meningeal inflammation infarction of lung myocardium mesentery spleen or kidney or *occlusion of peripheral arteries In right sided endocarditis* or patent ductus endarteritis emboli are carried to the lungs these may be responsible for an erroneous diagnosis of pneumonia

The *course* of subacute bacterial endocarditis is variable and may last from 1 month to 2 years Before effective methods of treatment were available the majority of patients died within 9 months of the onset

Intercurrent infections are not very common although bronchopneumonia occurs occasionally In rheumatic subjects the development of arthritis produces a clinical picture which may be indistinguishable from acute rheumatic fever

Since the introduction of penicillin therapy which controls the infection in most instances the principal *cause of death* in subacute bacterial endocarditis is progressive intractable cardiac decompensation This is probably the result of valvular damage which renders the heart mechanically less efficient together with myocarditis and increased demand for cardiac work occasioned by fever and anemia Some patients die following *cerebral myocardial* or mesenteric embolism while others succumb to a progressive toxemia of infection without localizing manifestations Rarely death is due to uremia caused by a progression of the nephritis this is more likely to occur in the relatively inactive cases Sometimes coma and death are the result of multiple small cerebral emboli which do not give localizing signs

Laboratory Findings The *leukocyte count* in the peripheral blood is usually moderately elevated but may be within the normal range *Circulating macrophages* may be found in smears of the peripheral blood These are thought by some hematologists to be of diagnostic value In cases of long standing a moderately severe normochromic *anemia* may be present There may be an *increase in serum globulin* and *cold precipitable globulins* are found in some cases The erythrocyte *sedimentation rate* is elevated Microscopic hematuria is very common and is helpful in diagnosis Albumin may also be found in the urine The *blood culture* is positive for *Streptococcus viridans* in about 80 per cent of cases *In these cases the number* of colonies of bacteria per milliliter of blood is usually approximately the same from day to day In a minority of instances the *blood* culture is consistently negative for reasons which are not clear It may be that in these cases the bacteria grow more deeply in the vegetations and hence do not have free access to the circulating blood It is often said that bacterial endocarditis located on the right side of the heart is more likely to be associated with negative blood cultures but there is little foundation for this assertion Actually it is not at all uncommon for bacteremia to be present in cases of right sided bacterial endocarditis

Differential Diagnosis The diagnosis of subacute bacterial endocarditis may be very easy or may be extremely difficult depending on the prominence of the various manifestations In a patient with the cardinal manifestations of fever heart murmur splenomegaly petechiae and clubbing of the fingers the diagnosis is obvious On the other hand subacute bacterial endocarditis can be a most difficult diagnostic problem since it can simulate a variety of diseases *The possibility of subacute bacterial endocarditis should be considered in every patient with fever and heart murmur* The diagnosis is missed most often in elderly patients especially those whose presenting complaint is the result of a cerebral embolic accident in such individuals a diagnosis of cerebral thrombosis or hemorrhage is likely to be made and little consideration given to the presence of a systolic murmur or low grade fever Heart murmur is so constantly present in the established disease (99.2 per cent of Kelson and White s series of 250 cases) that the diagnosis of subacute bacterial endocarditis can be excluded fairly safely in patients without murmurs An exception to this is the not infrequent absence of a murmur in early infections of the aortic valve in such cases a typical murmur may appear during treatment

This disease is one of the classic causes of "fever of undetermined origin " the important differential diagnostic points of which are covered elsewhere (p 72) Chief among the disorders which can be confused with it are systemic lupus erythematosus Hodgkin s disease miliary tuberculos s brucellosis periarteritis nodosa and acute rheumatic fever

Prognosis The natural course of the disease almost invariably leads to death the incidence of spontaneous recovery being less than 1 per cent In the past many forms of therapy were tried but found ineffective these included transfusions from immunized donors autogenous vaccines antiseptic drugs irradiation of the heart valves and so on With sulfonamide therapy a small proportion of patients probably not more than 4 per cent of those treated recovered The advent of antibiotic treatment brought about a great change in outlook and at present about 70 per cent of these infections can be brought under control Factors which point to

a favorable outcome in order of importance are penicillin sensitive organism freedom from signs of heart failure positive blood culture and short duration of illness

Treatment The following general statements deserve emphasis

1 Eradication of the infection requires employment of chemotherapeutic agents which exert a bactericidal action presumably because in their protected location the organisms must be killed without the aid of phagocytosis

2 Penicillin is the antibiotic of prime importance The special properties which make it so valuable in this situation are that huge doses can be tolerated by man that it diffuses into the vegetation in high concentration that organisms do not rapidly develop resistance to it and most important of all that it can be bactericidal and can eradicate the causative organisms without aid of phagocytes With most other antibiotics the situation is less favorable Even though capable of inhibiting bacterial growth in vitro the bacteriostatic antibiotics such as the tetracyclines and chloramphenicol rarely achieve a cure in this infection Therefore even when sensitivity tests indicate that the organism is as sensitive or even more sensitive to some other antibiotic penicillin may be the only agent capable of eliminating the infection

3 Streptomycin almost worthless when used alone has a place in treatment as an adjunct to penicillin This pertains especially to infections due to enterococcus which is relatively resistant to penicillin alone In the case of other varieties of *S viridans* the value of the combination therapy is less certainly established but since it may be beneficial and almost certainly does not detract from the efficacy of penicillin current practice in most places is to use both drugs in all cases of *S viridans* endocarditis

4 In an occasional case either because the organism is totally unaffected by penicillin (and streptomycin) or because the patient is so allergic to penicillin that this therapy in itself would threaten his life some other antibiotic regimen has to be employed Sensitivity tests with various combinations of antibiotics with special attention to bactericidal effect must be employed Bacitracin and neomycin despite the greater risk of toxic reaction are likely to be preferable to chloramphenicol or the tetracyclines Erythromycin and novobiocin may be effective especially when combined with other drugs

5 Antibiotic treatment must be continued for a considerable period of time In early experience with penicillin the impression was formed that treatment had to be maintained for 6 to 8 weeks and some authorities still regard this as the safest practice in all cases However later experience based upon use of much larger daily doses of penicillin in combination with streptomycin indicates that courses of treatment of 2 to 4 weeks are sufficient in most instances These shorter courses are justified in cases where the duration of illness is less than 3 months the organism is sensitive to penicillin and where there is prompt clinical improvement following the beginning of treatment Without these favorable indications it is safest to continue treatment for up to 8 weeks

Since the diagnosis can often be made with reasonable certainty on clinical grounds before bacteremia can be demonstrated and since in perhaps 20 per cent of cases blood cultures remain negative the question which often arises is how soon to begin chemotherapy An accurate bacteriologic diagnosis including antibiotic sensitivities is of great value and should be achieved if possible but undue delay of treatment must be avoided because of the possibility of embolic accident and progressive destruction of a cardiac valve A reasonable practice is to collect 4 to 6 blood cultures during a 48 hr period then begin treatment with penicillin and streptomycin observing the clinical response and modifying the chemotherapeutic regimen later as dictated by bacteriologic findings

When the infecting organism is penicillin sensitive a suitable dosage schedule is 2 400 000 units penicillin and 1 Gm streptomycin per day If the clinical response is not satisfactory or if the organism is only slightly sensitive to penicillin very much larger doses of penicillin up to 100 000 000 units per day may have to be given The dosage of streptomycin probably should seldom exceed 2 Gm per day The administration of very large amounts of penicillin is technically difficult since the pain of intramuscular injections is often severe and their intravenous administration may cause chemical phlebitis In order to maintain such a program of treatment for several weeks it is usually necessary to employ a variety of methods including continuous and intermittent intravenous and intramuscular injections Adjuvants such as Benemid may be used to reduce the rate of excretion of penicillin by the kidneys Ingenuity technical skill and stubborn persistence on the part of the doctor may be life saving

Embolic accidents resulting in hemiplegia mesenteric infarction or occlusion of a peripheral artery may take place many days after the beginning of effective antimicrobial therapy

The course of the fever after beginning chemotherapy is somewhat variable In most instances there is a defervescence within the first day or two but sometimes even when the end result is satisfactory a low grade fever continues for as long as 2 or 3 weeks

The treatment of congestive heart failure in bac

terial endocarditis does not differ from that of other kinds of congestive heart failure (see p 1304)

In infections located on patent ductus arteriosus or arteriovenous fistula cure can sometimes be achieved by surgical excision or obliteration of the fistulous tract Such operative treatment can be carried out during or at the conclusion of an appropriate course of chemotherapy

Relapse may occur after the cessation of penicillin therapy especially when the period of treatment has been short The great majority of relapses occur within the first 4 weeks after cessation of treatment It is usually safe to consider a patient s infection eradicated if he is free of symptoms and signs of the disease and if his blood cultures show no growth 6 weeks after the conclusion of therapy A recrudescence after that time may be due to a new infection rather than to persistence of the initial one

In the event of relapse additional chemotherapy is indicated It is particularly important to check the sensitivity of the infecting organism and to adjust the dose of penicillin or other antibiotic accordingly

Persons who have recovered from subacute bacterial endocarditis should be given prophylactic penicillin therapy before any operative procedure in an infected area such as tonsillectomy or tooth extraction It is advisable to administer penicillin orally in a dosage of one million units daily for 2 days prior to the procedure and for one day afterward

OTHER ETIOLOGIC AGENTS IN BACTERIAL ENDOCARDITIS

Although streptococci of the *viridans* type are by far the commonest cause of bacterial endocarditis accounting for approximately 90 per cent of all cases a wide variety of other microorganisms may be the cause of subacute or acute bacterial endocarditis These include nonpathogenic bacteria such as *S albus Hemophilus parainfluenzae* which give rise to the subacute pattern of disease just described and many genuinely pathogenic organisms such as *S aureus S pyogenes Brucella* the gonococcus meningococcus and pneumococcus which are likely to give a more fulminating disease picture In addition to bacteria certain of the fungi such as *Histoplasma capsulatum* have been shown to cause bacterial endocarditis

The term *acute bacterial endocarditis* is usually given to those cases in which the etiologic organism is a true pathogen such as *S aureus* or the pneumococcus and in which the course is relatively rapid—i e a few weeks This type of infection may involve previously normal valves hence a heart murmur may not always be present at the onset of illness The clinical picture is characterized not only by a short course but also by high fever multiple petechial hemorrhages and other embolic manifestations development of metastatic abscesses in other parts of the body and rapid destruction of the heart valve

The results of chemotherapy in these fulminating infections are still unsatisfactory Probably not more than 20 per cent of patients with acute staphylococcal or pneumococcal endocarditis recover even though the organism may appear to be sensitive to penicillin in the test tube Autopsies often reveal healing of the ulcerative endocarditis but the presence and persistence of one or more abscesses elsewhere Especially noteworthy are myocardial abscesses located in the region of the valve ring Apparently the sterilization of infection in such an abscess is very difficult to achieve with chemotherapy and this seems to be one of the reasons for the poor results obtained in this disease

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146 PYOGENIC INFECTIONS OF THE NERVOUS SYSTEM

John N Walton

Since many of the infective disorders of the central nervous system have already been dealt with elsewhere this chapter will be limited to a discussion of specific neurologic syndromes which arise when pyogenic bacteria or their products encroach upon nervous tissue It is proposed to consider the neurologic effects of suppuration within the cranial cavity or vertebral canal and to mention briefly certain particular neurologic aspects and complications of meningitis

Pyogenic organisms may gain access to the cranial cavity or spinal canal in a number of ways So far as the cranium is concerned direct spread of an infective process beginning in the middle ear or in

a paranasal sinus may give an osteomyelitis of cranial bones This in turn will often affect the extradural space whence further spread is possible through the meninges to the brain itself Septic thrombosis of diploic and emissary veins may play an important part in the process In the vertebral column osteomyelitis of a vertebra may play a similar role The next most frequent source of suppuration around or within the neuraxis is metastatic infection with blood borne organisms arising from a remote septic focus often in the skin or lung Lymphatic spread from a nearby locus of infection may account for certain cases of intraspinal suppuration but is virtually unknown as a cause of intracranial abscess formation In other cases organisms may be introduced by foreign bodies such as projectiles while rarely faulty aseptic technique in such procedures as lumbar puncture o cranial exploration may be responsible Of all the mechanisms described direct spread from the enveloping bony cage and metastatic infection are by far the most common in civilian medical practice

NEUROLOGIC ASPECTS OF BACTERIAL MENINGITIS

Bacterial meningitis as typified by that due to the meningococcus is regarded by many as a disease in which the pathologic changes are limited to the subarachnoid space and do not encroach upon nervous tissue It is also generally believed that these changes are entirely reversible with adequate treatment While both these views have considerable substance it is also true that sometimes lasting disability or a fatal outcome is due not to the meningitis but to certain distinctive pathologic changes which the disease produces in the nervous parenchyma Indeed it is probable that such changes may be far more frequent than is generally realized Similarly certain other neurologic manifestations are now known to depend upon vascular changes which are a part of the inflammatory process while others as well as some common sequelae may be attributed to incomplete resolution of the meningeal inflammation

Having accepted these generalizations it is possible to say that modern antibiotic and chemotherapeutic methods of treatment have greatly reduced the incidence of complications particularly in meningococcal meningitis However they are still of considerable importance in the other forms which show a less uniformly favorable response to treatment In tuberculous meningitis they are an outstanding feature

It is perhaps justifiable to consider the pathologic findings in fatal cases of influenzal meningitis as typifying the changes observed There are wide variations in the pathologic picture which can probably be related in most cases to the duration of the illness but in others are dependent on numerous factors particularly the resistance of the patient and the efficacy of treatment

The outstanding changes may be classified as follows

1 Subdural effusions serous or purulent
2 Severe brain swelling with tentorial or cerebellar herniation
3 Acute hydrocephalus without blockage of cerebrospinal fluid pathways
4 Ischemic necrosis of cerebral cortex or in more chronic cases nerve cell degeneration with marked glial reaction
5 Subependymal perivascular cellular infiltration with astrocytic and microglial proliferation
6 Subpial degeneration of spinal cord superficial as well as irregular parenchymatous degeneration of cranial and spinal nerves
7 Vascular changes
   a Cortical thrombophlebitis
   b Endothelial swelling and cellular infiltration in meningeal arteries in some cases there is a severe arteritis leading to thrombosis
8 Organization of exudate with meningeal fibrosis

Subdural empyema is a relatively uncommon complication of bacterial meningitis and will be considered in detail shortly ***Serous subdural effusions*** have been recognized recently as an important complication of meningitis in infancy McKay Ingraham and Matson found such collections in 60 per cent of all patients under 1 year of age who were suffering from meningococcal influenzal or pneumococcal meningitis They suspect that such collections may be present if any of the following features are noted (1) persistent high temperature after 72 hr of adequate treatment (2) positive cerebrospinal fluid culture after 48 hr of treatment (3) convulsions during convalescence (4) focal convulsions at any time (5) vomiting during the convalescent period (6) gross neurologic abnormality (7) clinical impression that the course is unsatisfactory Any one of these findings is they believe an indication for aspiration of the subdural space carried out by needling in the lateral angle of the anterior fontanel If a subdural effusion is present fluid will readily be withdrawn It is always xanthochromic and may even be frankly bloody it usually contains up to 2 or 3 Gm per 100 ml of protein and several hundred white cells per cubic millimeter It is sterile on culture in most cases Many workers believe that this complication is best treated by daily aspiration while antimicrobial therapy is continued Others however suggest that in these patients a subdural membrane similar to that of chronic subdural hematoma is

present and should be removed surgically McKay Ingraham and Matson believe that if such a mem brane is left it will interfere with the growth of the brain In the absence of any conclusive evidence that this does in fact occur it seems that repeated aspiration is the treatment of choice and that surgery should be reserved for those cases which fail to respond to this regimen

In a proportion of the cases of acute meningitis which die within 24 to 48 hr of the onset an *acute brain swelling* or alternatively *hydrocephalus* may be seen producing fatal tentorial or cerebellar herniation The exact cause of these changes is un known though they seem to be related in some way to the acuteness of the disease process

The etiology of the cortical and subependymal changes is also obscure The diffuse nerve cell de generation and subpial glial reaction are probably evidence of a *noninfectious encephalomyelopathy* due to a number of circulatory and toxic factors but the subependymal changes may be the result of direct bacterial invasion This encephalopathy is probably responsible for the stupor coma and the generalized convulsions of the disease The areas of *cortical necrosis* probably explain many of the focal neurologic symptoms and signs such as focal sei zures or hemiplegia Pain in the limbs blindness and deafness or other cranial nerve palsies can be attributed to *degenerative changes in the nerves or roots* Chronic meningeal fibrosis so-called *ad hesive arachnoiditis* may sometimes produce simi lar effects as a late sequel through constriction of nerve trunks

The *arterial infiltration* already described does not appear to be responsible for important nervous lesions in pyogenic meningitis *Thrombophlebitis* may give rise to focal convulsions neurologic signs or subarachnoid bleeding through cortical infarc tion The thrombophlebitis is generally aseptic and occasionally involves the sagittal sinus giving a syndrome which will be discussed later in this chapter

Meningeal fibrosis and organization of exudate can block the aqueduct the foramens in the roof of the fourth ventricle or the tentorial hiatus Ob structive or communicating hydrocephalus results Similar dense meningeal thickening around the brain stem may sometimes be responsible for the tonic spasms which occasionally accompany and follow meningitis and it is conceivable that they may even be the basis for the terminal decere brate state of some such patients

Although these changes have been most care fully studied in influenzal and pneumococcal men ingitis it is probable that the complications and sequelae of most forms including tuberculous meningitis are similarly determined Tuberculosis may be complicated by infarction due to arterial occlusion since the basal arteritis which has been well described by Doniach is more striking in this than in other types of meningitis

INTRACRANIAL SUPPURATIVE DISORDERS

If bacterial meningitis is excluded it can be said that suppurative disease within the cranial cavity occurs in one of five situations The process may occur external to the dura in which case an *extra dural abscess* results or it may penetrate the dura to give a *subdural abscess* or *empyema* very rarely a localized *subarachnoid abscess* may occur within the subarachnoid space In other instances the in flammation may affect principally an intracranial venous sinus or its radicals giving *suppurative thrombophlebitis* Most commonly of all the inflam matory process involves brain tissue beginning as a diffuse process of *suppurative encephalitis* This inflammatory process may continue to spread until the patient dies but more often the infected area or areas become surrounded by reactive tissue to give one or more *brain abscesses*

Practically all extradural and subdural abscesses and more than 50 per cent of brain abscesses are produced by centripetal spread of suppuration from the cranial bones

Extradural Abscess

The cranial osteomyelitis responsible for produc ing an extradural abscess is generally due to otitis media sinusitis or trauma Pus accumulates on the inner side of the cranium and strips off the dura which becomes lined on its external surface by a layer of granulation tissue An abscess in this situa tion is difficult to diagnose since it is rarely large enough to produce a severe increase in intracranial pressure or focal neurologic signs It may however be suspected in the presence of irregular pyrexia and headache which radiates from either the mas toid (in otitis media) or frontal region (in frontal sinusitis) there is often marked tenderness of the skull in the affected region The cerebrospinal fluid may be normal but usually shows a slight poly morphonuclear or mononuclear pleocytosis This condition can be treated effectively by antibiotic therapy and surgical drainage

Subdural Abscess or Empyema

This syndrome is usually a complication of frontal sinusitis it sometimes occurs in otitis but is rarely metastatic

In most cases infection of the subdural space is effected by direct extension through the dura but in others it is the result of septic thrombophlebitis of venous sinuses particularly the superior longi tudinal The subdural pus usually covers the greater part of the lateral surface of the affected hemisphere

and tends to accumulate over the lateral aspect of the frontal lobe In fatal cases ischemic necrosis of subjacent cortical gray matter is found and thrombosis of subarachnoid and cortical veins is frequent

The symptomatology of this disease follows a relatively stereotyped pattern When it complicates sinusitis there is usually exacerbation of frontal pain and nasal discharge followed by orbital swelling headache is at first localized to the frontal region but later becomes generalized and increases in severity Concurrently high fever neck stiffness and drowsiness or stupor develop and are followed by focal neurologic signs Jacksonian seizures are common aphasia is seen in left sided lesions paralysis of contralateral ocular deviation is frequent and all patients have a *hemiparesis* or *hemiplegia* Clinical manifestations in cases not caused by sinusitis are identical save for the absence of signs of sinus infection and orbital swelling

Most cases show a marked increase in cerebrospinal fluid pressure and the total protein content is raised often to about 100 mg per 100 ml though the sugar remains normal and the fluid is sterile on culture A cell count of several hundred per cubic millimeter is usual and the majority of the cells are *polymorphonuclear leukocytes*

If not treated the condition is fatal within about 10 to 14 days after the onset of headache or 3 to 4 days after the accession of focal neurologic signs Effective treatment consists in administration of the appropriate antibiotic combined with drainage of the abscess through one or more burr holes Attempts to drain the abscess through the frontal sinuses or ear almost invariably fail

It is sometimes difficult to distinguish this condition from intracranial thrombophlebitis or from necrotizing encephalopathy with predominant involvement of one hemisphere

Intracranial Thrombophlebitis

This most often affects the lateral cavernous or superior longitudinal sinuses owing to centripetal spread of infection from the middle ear the skin of the face or the frontal sinus respectively In all three conditions the patients are acutely ill with high remittent fever

In *lateral sinus thrombosis* there is usually headache in the temporal region Papilledema may sometimes occur but focal neurologic signs are generally absent and the clinical picture is dominated by the manifestations of pyemia Compression of the homolateral internal jugular vein may produce no rise in pressure during spinal manometry whereas a normal rise occurs during compression on the opposite side (Tobey Ayer test)

Cavernous sinus thrombosis gives homolateral frontal headache and facial pain followed by proptosis edema of the eyelids chemosis and paresis of oculomotor nerves Often the infection spreads through the circular sinus to the other cavernous sinus This may sometimes be prevented by early treatment

Suppuration within the *superior longitudinal sinus* usually produces headache and marked papilledema with edema and engorgement of the scalp over the vertex A monoplegia of one leg or a paraplegia may result from infarction of the leg area or areas of the motor cortex but this is uncommon More often a subdural empyema results

Septic thrombosis in any of the three situations requires vigorous chemotherapy and this is the only method of treatment in cavernous sinus disease Surgical exposure and drainage of the lateral sinus or ligation of the internal jugular vein may sometimes be required

Aseptic thrombosis of intracranial venous sinuses particularly the lateral and superior longitudinal is an occasional complication of otitis media and in many such cases there is no evidence of intracranial spread of microorganisms The resulting syndrome is characterized by severe papilledema and increase in the intracranial pressure with comparatively little headache it has been called *otitic hydrocephalus* by Symonds In severe cases (when the process extends to cortical veins) seizures focal neurologic signs and even profuse subarachnoid hemorrhage may result from cortical infarction An identical syndrome not uncommonly occurs in marasmic infants in cachectic patients during pregnancy following closed head injury or in individuals with heart disease or blood dyscrasias

Brain Abscess

Incidence Brain abscess may occur at any age and is equally common in the two sexes It is probable that fewer cases of otitis and intrathoracic suppuration have been complicated in this way since the advent of antibiotic therapy but certain patients who would previously have died from the primary infection now survive to develop a brain abscess

Etiology and Location About 40 per cent of brain abscesses are secondary to middle ear disease and of these about a third arise in the anterior part of the lateral cerebellar lobe the remainder lying in the middle part of the temporal lobe above the tegmen tympani Frontal sinusitis accounts for roughly 10 per cent of cases and the abscess is almost invariably situated in the anterior part of the frontal lobe Of the remaining 50 per cent of cases a small proportion are due to penetrating wounds and the remainder are metastatic in about half of these the primary septic focus is in the lung (bronchiectasis empyema lung abscess) and in

the others it may be in the skin or other diverse locations such as bone or the heart Brain abscesses are particularly frequent in patients with congestive heart failure or cyanotic congenital heart disease even without evidence of bacterial endocarditis In traumatic cases the site of the abscess will clearly depend upon the area which has been traumatized but a metastatic abscess may be situated anywhere within the cranium though it is usually above the tentorium Most lie within the distribution of the middle cerebral artery beginning at the junction of the gray and white matter they are not infrequently multiple or multiloculated a finding which is less frequent in the case of otitic abscesses

Almost any of the common organisms may cause a cerebral abscess the most frequent being streptococci pneumococci and staphylococci while fusiform bacilli and oral spirochetes are sometimes found Less commonly such organisms as *Endamoeba coli Actinomyces* or even *E histolytica* may be responsible

Pathology Invasion of nervous tissue by the causal organism leads initially to focal necrosis and liquefaction accompanied by edema of the surrounding brain this stage is called *suppurative encephalitis* If the patient survives pus accumulates and a capsule begins to form from fibroblasts derived from proliferating capillaries In due course a firm thick fibrous capsule forms and may be several millimeters in diameter it is lined by a layer of granulation tissue containing polymorphonuclear leukocytes histiocytes lymphocytes and proliferating capillaries In brain tissue surrounding the fibrous wall are found reacting microglia fibroblasts and astrocytes in profusion

Clinical Manifestations The physician should be aware of the many ways in which a brain abscess may develop for early diagnosis is the key to effective treatment Early in the illness the patient s symptoms are all important since physical signs may not develop until a relatively late stage When a known sufferer from otitis media experiences a suppression of aural discharge following a period of exacerbation and this is succeeded by headache vomiting and confusion it is reasonable to suspect that inflammation has spread intracranially In many cases however the symptoms are not striking and the patient may seem to recover from a flare up of his otitis but remains unwell experiencing attacks of depression and irritability vague intermittent headache and nausea anorexia weight loss and mild fever Symptoms and signs of meningeal irritation are usually minimal A history of this type in a patient with paranasal sinusitis should also make one suspicious of intracranial suppuration the cerebrospinal fluid should be examined immediately

In hematogenous abscess the onset is sometimes dramatic with sudden focal seizures and neurologic signs followed after an interval of days or weeks by increasing pyrexia and evidence of mounting intracranial pressure This may be seen when an infected embolus becomes impacted in a large vessel Far more often however the onset is insidious with minimal headache slight intermittent pyrexia and gradual personality change When there is an evident septic focus in the skin or lung the possibility of abscess may spring to mind but in many other instances the patient may be felt to be suffering from an intracranial tumor This is particularly common when antibiotic therapy effectively masks the patient s symptoms throughout the stage of suppurative encephalitis

When the clinical manifestations of brain abscess are more fully developed they fall into three groups (1) general symptoms of infection (2) symptoms and signs of increased intracranial pressure and (3) focal symptoms and signs

The severity of the *general symptoms of infection* is related to the acuteness of the disease process In cases of acute suppurative encephalitis they may be severe in patients in whom the onset is more insidious a low intermittent pyrexia is the rule while in more chronic cases the temperature may be normal throughout

Some evidence of *increased intracranial pressure* is usually found although in a few patients with large chronic abscesses it may be lacking In general the patients have headache which may occasionally be localized over the area of suppuration More often it is of the type usually seen in increased intracranial pressure being paroxysmal worse in the mornings and increased by movement Nausea is frequent and is followed by vomiting in the later stages The pulse is more likely to be slow in patients with abscess than in any other form of intracranial disease Papilledema is usually a late sign but mental changes consisting of mild confusion and irritability or other change in temperament progressing to severe confusion drowsiness stupor and coma are commonly present

Temporal Lobe Abscess If the abscess affects the dominant hemisphere dysphasia which is often of nominal" or "amnesic type is frequent the patient finds difficulty in naming familiar objects A homonymous upper quadrantic field defect is often seen because of involvement of the optic radiation Evidence of pyramidal tract involvement is usually minimal and may be little more than slight contralateral facial or finger weakness though extensive lesions may give a hemiparesis Herniation of the temporal lobe through the *tentorial hiatus* may lead to a homolateral third nerve palsy to

coma and to signs of bilateral disease of the pyramidal tracts.

Cerebellar Abscess. Headache in the suboccipital region is common, and the neck may be stiff or held to one side. Evidence of increased intracranial pressure is often more striking in these patients than in those with abscesses situated elsewhere. Signs of cerebellar deficiency such as hypotonia, incoordination, past pointing, and slow performance of rapid alternating movements may be seen in the limbs on the affected side. The patient may tend to fall or stagger to this side on walking. Nystagmus is usually present, being most marked on lateral gaze to the side of the lesion; there may also be compression of the brain stem leading to cranial nerve pareses and contralateral pyramidal signs, but these manifestations are most variable. Homolateral pyramidal signs may occur, due probably to compression of the contralateral cerebral peduncle against the free edge of the tentorium.

Frontal Lobe Abscess. Patients with frontal lobe abscess often show no focal neurologic signs. Headache, drowsiness, and impairment of memory, attention, and intellectual function are prominent. In some cases there is a grasp reflex and contralateral deviation of the head and eyes. If the abscess is large, a hemiparesis and dysphasia (in dominant hemisphere lesions) may result.

Diagnostic Procedures. Examination of the *cerebrospinal fluid* may be of great diagnostic value, but this procedure should be carried out with care, particularly in those cases in which a temporal or cerebellar abscess is suspected. In such a case, removal of even a moderate quantity of fluid can lead *to herniation of the temporal lobe through the* tentorial hiatus or of the cerebellum through the foramen magnum with fatal results. Whenever there is evidence of increased intracranial pressure, only a small amount of fluid should be removed, and in the presence of marked papilledema the procedure is contraindicated. The fluid usually shows an increased pressure, and its protein content is often higher than 100 mg per 100 ml; it rarely contains more than 100 white cells per cubic millimeter, and the majority are mononuclear, though a number of neutrophils may be present in the early stages. The sugar content of the fluid is normal, and no bacteria are seen in smears or isolated by culture. *Electroencephalography* may be of considerable value in diagnosis and localization, since an abscess in one cerebral hemisphere usually gives a focus of extremely slow and irregular delta activity of high amplitude. *Radiography* of the skull may show displacement of the pineal body. *Angiography* may localize it accurately, but many surgeons prefer *ventriculography*. *Air encephalography* by the lumbar route is dangerous when the intracranial pressure is raised. After treatment of the abscess, instillation of Thorotrast into the cavity may demonstrate its progressive decrease in size.

Diagnosis. In the chronic abscess with no clear primary focus of infection, differentiation from intracranial tumor may be impossible except by cerebrospinal fluid examination or exploration. In the more acute cases, the condition is distinguished from meningitis by the absence of meningeal irritation and by the cerebrospinal fluid changes. In patients with otitis media there may be confusion between temporal abscess and lateral sinus thrombosis, or between cerebellar abscess and labyrinthitis. However, septic thrombosis of the lateral sinus is usually a more dramatic febrile illness than temporal abscess and rarely produces focal neurologic signs; in a proportion of cases the Tobey-Ayer manometric test will be positive. Labyrinthitis can usually be recognized, since it tends to give more vertigo and less headache than does cerebellar abscess and does not produce papilledema or changes in the cerebrospinal fluid.

Prognosis. Without treatment, brain abscess is an almost uniformly fatal disease save for the very rare cases which become quiescent and thickly encapsulated and a few in which spontaneous drainage occurs via the middle ear or frontal sinus. Death usually results from diffuse suppurative encephalitis, increased intracranial pressure, brain herniation, or from rupture of the abscess into the ventricular system or subarachnoid space. Before the days of antibiotics about 50 per cent of patients died despite surgical treatment; after penicillin became freely available, the mortality rate *dropped to under 30 per cent.*

Late Prognosis. Not all the 70 per cent of patients who survive after treatment of a brain abscess recover completely. Some are left with signs of neurologic deficit, varying from a mild field defect to hemiplegia. Recurrent headaches, intellectual impairment, and anxiety states are common, and about 50 per cent of surviving patients develop seizures as a sequel.

Treatment. During the stage of acute suppurative encephalitis, to carry out an intracranial operation is to court disaster through wider dissemination of the inflammatory process. In this stage every attempt should be made to isolate the responsible organism from either the cerebrospinal fluid or the primary septic focus. Vigorous antibiotic therapy with the appropriate agent, systemically and if possible intrathecally, is indicated. Sometimes a patient who appears to have all the typical symptoms and signs of a brain abscess recovers on medical therapy alone. The great majority, however, require surgical intervention. Occasionally in the presence of deepening coma and progressive neuro

logic signs operation may be necessary even in the acute stage More often it is possible to wait until the inflammatory process has become localized All abscesses presenting in the chronic stage should be operated upon promptly Details of surgical treatment are beyond the scope of this volume but it can be said that some surgeons prefer to aspirate the abscess and instill antibiotics while others believe in its total extirpation In the former method *it is easy to overlook multiple abscesses or separate* loculi and recurrences are possible but extirpation may leave more severe sequelae than would have occurred after aspiration Both methods have proved successful in the hands of their proponents

INTRASPINAL SUPPURATIVE DISORDERS

Of the suppurative conditions within the spinal canal epidural abscess is the commonest by far Very rarely an abscess may form within the subdural space following a penetrating wound or localization of a purulent meningitis however its clinical manifestations do not differ significantly from those of epidural abscess and in both conditions surgical exploration is required *Intramedullary spinal abscess* is also extremely rare it is almost invariably metastatic in origin tends to run a more rapid course than most cases of epidural suppuration and is attended by less pain than is the latter It often presents with paresthesias in the lower limbs followed by progressive flaccid paralysis Many cases of this type cannot be distinguished from other forms of acutely progressive myelopathy and few are diagnosed during life Foley has pointed out that the diagnosis may be suspected when clinical manometric and radiologic findings suggest an intramedullary tumor and there is also a clear focus of infection elsewhere in the body In such cases improvement and certainly survival may follow aspiration or incision and drainage of the abscess together with antibiotic therapy In view of the rarity of subdural and intramedullary suppuration in the spinal canal they will not be considered further Nor will tuberculous epidural abscess be given separate consideration since its presentation *and management are best considered* along with tuberculous spinal disease

Spinal Epidural Abscess

The recognition of this condition is a matter of paramount importance since surgical intervention in the early stages is usually rewarded by total recovery whereas even brief delay may lead to paraplegia quadriplegia or death There are few disorders in which early diagnosis is so imperative and for this reason alone it merits detailed description

Etiology Vertebral osteomyelitis is the cause of this syndrome in about a third of cases Hematogenous spread from an infective focus often cutaneous sepsis and sometimes pyelonephritis are presumably responsible for most of the remaining cases Much more rarely the abscess may arise through lymphatic spread from a paraspinous lesion such as mediastinal or retropharyngeal abscess and it is also possible for it to be caused by direct inoculation (lumbar puncture needle) or by a penetrating wound Almost invariably *Staphylococcus aureus* is the responsible organism

Pathology Granulomatous tissue with a variable amount of pus tends to accumulate in the epidural fat over the dorsal aspect of the dura and to spread longitudinally In osteomyelitic *cases aggregations* of purulent material are often found in the lateral epidural regions in relation to the bony lesion but an anterior accumulation is rare owing to the intimate relationship of the dura and the intervertebral ligaments Large collections of pus *are uncommon* more often it is found as multiple small pockets in exuberant granulation tissue The inflammatory process may extend axially so as to overlie as many as seven bony segments but is usually limited to three or four extension is less marked in the osteomyelitic cases The inflammatory process may also spread laterally and dorsally to involve paravertebral structures spinal muscles and even subcutaneous tissue but anterior extension is virtually unknown Nor does the process often traverse the dura its effect upon the spinal cord seems to depend upon a combination of a simple compression and interference with the circulation *in epidural* veins leading to derangement of the medullary circulation

Clinical Manifestations Heusner has pointed out that although spinal epidural sepsis produces clinical syndromes which differ in tempo there is a basic clinical pattern common to all variants It consists of the following march of events

Phase I Spinal ache
Phase II Root pain
Phase III Weakness of { voluntary muscles / sphincters / sensibilities }
Phase IV Paralysis

Sometimes the symptoms and signs of severe *infection* may partially mask the above features but they are always present if looked for with care The initial aching pain is usually accompanied by fever and the *spine is tender in the affected region* Within 2 or 3 days root pains are added which radiate from the affected segment and the spine is then exquisitely tender If the *condition* remains untreated the general signs of infection *increase* the spinal ache *becomes* excruciating neck stiffness develops and soon afterwards weakness *ascending*

coma and to signs of bilateral disease of the pyramidal tracts

Cerebellar Abscess Headache in the suboccipital region is common and the neck may be stiff or held to one side Evidence of increased intracranial pressure is often more striking in these patients than in those with abscesses situated elsewhere Signs of cerebellar deficiency such as hypotonia incoordination past pointing and slow performance of rapid alternating movements may be seen in the limbs on the affected side The patient may tend to fall or stagger to this side on walking Nystagmus is usually present being most marked on lateral gaze to the side of the lesion there may also be compression of the brain stem leading to cranial nerve pareses and contralateral pyramidal signs but these manifestations are most variable Homolateral pyramidal signs may occur due probably to compression of the contralateral cerebral peduncle against the free edge of the tentorium

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Diagnostic Procedures Examination of the *cerebrospinal fluid* may be of great diagnostic value but this procedure should be carried out with care particularly in those cases in which a temporal or cerebellar abscess is suspected In such a case removal of even a moderate quantity of fluid can lead to herniation of the temporal lobe through the tentorial hiatus or of the cerebellum through the foramen magnum with fatal results Whenever there is evidence of increased intracranial pressure only a small amount of fluid should be removed and in the presence of marked papilledema the procedure is contraindicated The fluid usually shows an increased pressure and its protein content is often higher than 100 mg per 100 ml it rarely contains more than 100 white cells per cubic millimeter and the majority are mononuclear though a number of neutrophils may be present in the early stages The sugar content of the fluid is normal and no bacteria are seen in smears or isolated by culture *Electroencephalography* may be of considerable value in diagnosis and localization since an abscess in one cerebral hemisphere usually gives a focus of extremely slow and irregular delta activity of high amplitude *Radiography* of the skull may show displacement of the pineal body *Angiography* may localize it accurately but many surgeons prefer *ventriculography* *Air encephalography* by the lumbar route is dangerous when the intracranial pressure is raised After treatment of the abscess instillation of Thorotrast into the cavity may demonstrate its progressive decrease in size

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Prognosis Without treatment brain abscess is an almost uniformly fatal disease save for the very rare cases which become quiescent and thickly encapsulated and a few in which spontaneous drainage occurs via the middle ear or frontal sinus Death usually results from diffuse suppurative encephalitis increased intracranial pressure brain herniation or from rupture of the abscess into the ventricular system or subarachnoid space Before the days of antibiotics about 50 per cent of patients died despite surgical treatment after penicillin became freely available the mortality rate dropped to under 30 per cent

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Section 10 Fungous Diseases

Abraham I Braude

Except for their etiology fungous infections differ little from bacterial infections The close relationship between bacteria and fungi is apparent from transitional forms connecting the two classes and from the similarity of the pathologic changes and clinical manifestations induced by them

The intermediate or transitional forms are represented by the *Actinomyces* These possess the characteristic branched mycelium of fungi but divide by segmentation into gram positive bacillary or coccoid forms The acid fast property of one species *Nocardia asteroides* indicates a relationship to the tubercle bacillus Although actinomycosis and nocardiosis are placed among the fungous diseases in this book the causative agents remain in an uncertain position between fungi and bacteria

An important characteristic of pathogenic fungi is dimorphism growth in two distinct forms under different environmental conditions The fungi responsible for blastomycosis sporotrichosis and histoplasmosis assume unicellular yeast" forms in infected tissues but grow as mycelia and produce asexual spores on Sabouraud agar The reverse is true for the fungus causing moniliasis Another type of dimorphism is found in coccidioidomycosis The organism responsible for this infection is multicellular in vivo and in vitro but its form differs under the two conditions In the tissues it is a sac filled with multiple spores and the growth on agar is a segmented mycelium *Cryptococcus neoformans* is the only pathogenic fungus that fails to change form when environmental conditions vary

Mycotic diseases are not transmitted from one person to another Many fungous infections are acquired by inhalation of spores growing freely in nature These spores may be rectangular unicellular mycelial fragments known as *chlamydospores* or spherical bodies borne on thin mycelial stalks and called *conidia* Other infections such as sporotrichosis result from inoculation of spores directly into the skin

A few fungous diseases are endogenous in origin *Actinomyces bovis* is a normal anaerobic inhabitant of the mouth and *Candida albicans* is a normal resident of the bowel and mouth When the normal resistance of the host is reduced endogenous infection by either agent can develop Actinomycosis is often preceded by tooth extraction and overgrowth of normal saprophytic bacteria by *C albicans* in the course of antibiotic therapy can lead to moniliasis

The mechanisms whereby fungi produce disease are obscure *Cryptococcus neoformans* possess a polysaccharide capsule similar to that of the pneumococcus which seems to protect the yeast from phagocytosis This capsular material also produces mechanical injury in the nervous system It is possible that the thick walls of other fungi such as *Blastomyces dermatiditis* and *Coccidioides immitis* function similarly as a protection against leukocytes Some fungi are ingested by phagocytes but seem to flourish within these cells In histoplasmosis for example the parasites are found in enormous numbers within reticuloendothelial cells The endothelium of small vessels can become so packed with *Histoplasma* organisms that blood flow is compromised

Another possible factor in the pathogenesis of these infections is hypersensitivity In most fungous diseases the patient exhibits marked local or even systemic reactivity to intradermal injection of the causative organism In coccidioidomycosis this type of reaction is closely associated with the development of erythema nodosum and pleural effusions The occurrence of necrosis at the site of injection of fungous antigens suggests that hypersensitivity may be responsible for necrosis of infected tissues In other patients however widespread destruction of tissue can occur despite absence of dermal sensitivity

Despite the differences in morphology and life cycle of fungi and bacteria both elicit similar pathologic changes and clinical manifestations For this reason specific diagnosis can seldom be made with certainty without demonstration of the causative organism Fortunately most pathogenic fungi are easily seen in infected tissues or exudates In a few circumstances however it is necessary to rely upon epidemiologic and immunologic methods for diagnosis

The following chapters deal only with those infections in which fungi penetrate beneath the skin

numbness of the limbs and impairment of sphincter control appear Between this stage and that of ir reversible flaccid paralysis there may be an interval of only a few hours

Many authors distinguish the acute metastatic from the acute osteomyelitic syndrome on clinical grounds the interval between phase I and phase II is very much longer in the osteomyelitic cases lasting days or even weeks but thereafter the *disease progresses with extreme rapidity It is also* true that there occur occasional chronic cases in which the march of events and the clinical picture are both attenuated and the illness lasts weeks or months with much less pain and no general signs of infection Despite these variations there is no doubt that the condition presents as a well defined clinical syndrome the diagnosis must be made in phase II or early in phase III if the patient is to recover

Diagnostic Procedures While radiography of the spine may be of great value in diagnosis particularly of the osteomyelitic cases there will be many instances in which an epidural abscess is present before the characteristic radiologic changes of osteomyelitis have had time to develop The most important investigation is spinal puncture It must be stressed however that when this condition is suspect spinal puncture should be performed by a skilled individual who is fully acquainted with the pathology of the probable lesion Lack of adequate care may mean that the needle will carry organisms *from the extradural to the subarachnoid space* If the puncture is performed at the level of the lesion pus will be found in the epidural space if not there will be a complete manometric spinal block and the spinal fluid will be xanthochromic containing a large amount of protein and only a few white cells With a characteristic clinical picture either of these findings is a sufficient indication for surgical exploration

Diagnosis In phase I cases of this type are often dismissed as examples of arthritis lumbago or spinal strain In phases II and III however the characteristic combination of fever root pain and exquisite spinal tenderness *is sufficient to exclude* such conditions as prolapsed intervertebral disk meningitis poliomyelitis transverse myelitis and polyneuritis *In* the uncommon chronic cases differentiation from intrathecal neoplasm on clinical grounds may be difficult but the changes found on spinal puncture will indicate the need for surgical exploration

Treatment Once the diagnosis is established the great majority of cases require immediate laminec*tomy for drainage of the epidural space* and vigorous antibiotic therapy should be continued Very occasionally if the abscess is situated below the termination of the spinal cord there may be recovery with antibiotics alone Scrupulous observation is necessary and neurologic signs are an indication for immediate surgery

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ough search is made by diluting the pus with saline and filtering through gauze They are white yellow or brown and stand out sharply against the background of blood tinged pus The conclusive finding of course is the demonstration of gram positive filaments or bacilli which fail to grow aerobically on conventional laboratory media Granules of other organisms (staphylococci *Nocardia* *Monosporium*) fragments of caseous material and clumps of pus cells or fibrin may be confused with actinomycotic granules The technique for recovery of *A bovis* from the infected material differs from that of most other pathogenic fungi in two important respects (1) Animal inoculation is of no value and (2) Sabouraud medium will not support its growth Cultural isolation of *A bovis* is not difficult if any of several anaerobic methods is used Inoculation of Brewer s thioglycollate medium or glucose agar shake cultures is simple and satisfactory

Biopsy examination may establish the diagnosis if the actinomycotic colony ("ray fungus) is observed microscopically Demonstration of the organism can be exceedingly difficult requiring careful search of many sections

Intradermal or serologic tests with *A bovis* or its fractions are of no diagnostic aid Radiologic examination is rarely of specific value because the intrathoracic lesions resemble tuberculosis or tumor and those in bone cannot be distinguished from bacterial osteomyelitis

Treatment Penicillin and the tetracycline antibiotics are effective in treatment When either is administered in large doses over long periods of time remarkable improvement may be expected even when the purulent processes are inaccessible to surgical drainage Many recent reports indicate that the tetracycline drugs (chlortetracycline oxytetracycline tetracycline) are superior to penicillin When the tetracyclines are given in doses of 500 mg every 6 hr there is a reduction in pain and swelling within a few days as well as gain in strength increase in weight and prompt defervescence Treatment should be continued for at least a month or much longer if persistent lesions can be demonstrated by physical examination or radiologically Because penicillin is no more effective than the tetracyclines and because it requires repeated intramuscular or intravenous injection of large doses for long periods of time it should be reserved for those patients who cannot tolerate the tetracycline drugs The optimum dose of penicillin is not known At least 1 million units daily should be given intramuscularly for 4 to 6 weeks and longer if healing is still incomplete

Surgical drainage or excision of accessible actinomycotic lesions is a valuable adjunct to chemotherapy although surgery alone is of little value Older treatments such as iodides irradiation or the sulfonamides have no place in the current therapeutic regimen for actinomycosis

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148 CRYPTOCOCCOSIS

Abraham I Braude

Definition Cryptococcosis is a highly fatal infection caused by *Cryptococcus neoformans* an encapsulated yeast with a special predilection for the central nervous system Cryptococcosis can also involve the lungs bones and skin and occurs with increased frequency in patients with leukemias or lymphomas

Etiology Members of the genus *Cryptococcus* to which *C neoformans* belongs form neither mycelia nor spores and reproduce entirely by budding The cells of *C neoformans* are spherical measure 5 to 15 μ in diameter retain the Gram stain and are surrounded by a capsule which may become so large that its total diameter is three times that of the cell proper The capsular material contains a polysaccharide which is responsible for the slimy appearance of the yeast in culture and for the myxomatous character of cryptococcal lesions

The organisms grow readily on various media at room temperature and at 37 C On Sabouraud glucose agar visible growth appears within a few days at 37 C and gradually assumes a characteristic

and mucous membranes to involve the underlying tissues and viscera

147 ACTINOMYCOSIS

Abraham I Braude

Definition Actinomycosis is a noncontagious suppurative infection produced by an anaerobic organism normally resident in the mouth The disease is characterized by chronic inflammatory induration and sinus formation

Etiology The causative agent is a branching gram positive filamentous organism Attempts have been made to recognize two separate anaerobic species of the genus *Actinomyces* on the basis of their pathogenicity for man or cattle Those who would make this differentiation have designated *Actinomyces bovis* the culturally smooth form as the agent responsible for actinomycosis in cattle and *A israeli* the rough form as the etiologic agent of human actinomycosis Because these smooth and rough forms are probably variants of the same species the term *Actinomyces bovis* will be used here for all pathogenic anaerobic actinomyces

Actinomyces bovis differs from all other actinomyces in its intolerance of free oxygen and its failure to grow on Sabouraud s medium It also has a much greater tendency to fragment into short gram positive rods (arthrospores) On blood agar colonies require 4 to 6 days of anaerobic incubation at 37 C to reach a size of 1 to 2 mm Although most strains require anaerobic conditions for isolation some can be subcultured aerobically in 10 to 20 per cent carbon dioxide *A bovis* has never been found outside the human or animal body and case to case transmission has never been known to occur

Pathogenesis The saprophytic actinomyces produce disease only under circumstances which favor the growth in the tissues The oxidation reduction potential of normal tissues is probably too high for the multiplication of *A bovis* but in devitalized tissues it reproduces and gains a foothold from which it can spread The frequency of actinomycotic lesions of the face and neck may be explained not only by the greater population of *A bovis* in the pharynx but also by the frequent trauma to which these tissues are subjected by eating by dental procedures or by infection with oral bacteria Appropriate anaerobic conditions are also present in atelectatic areas of the lung after aspiration and *A bovis* sometimes predominates among the aspirated organisms and produces pulmonary actinomycosis It is also possible that pulmonary actinomycosis may be hematogenous in origin an infected area in the mouth serving as the primary site The exact mode of development of abdominal actinomycosis is unknown but the frequency with which the cecal region is involved suggests that the conditions here favor devitalizing injury Occasionally perforation by a foreign body precedes infection

From foci in the jaw lung or bowel actinomycosis may spread by contiguity or through the blood to the liver spine brain kidneys internal genitalia spleen and subcutaneous tissues

The inflammatory reaction to *A bovis* is characterized by three features (1) granulomas (tubercles) containing multinucleated giant cells (2) extensive necrosis and (3) intense fibrosis The so called "sulfur granules which occupy a prominent place in the inflammatory lesion of actinomycosis are composed of intertwined mycelial filaments

Clinical Manifestations The essential feature of actinomycosis is a painful indurated swelling This lesion may appear over the jaw a week or more after such trauma as tooth extraction or compound fracture of the mandible As it increases in size points of suppuration the openings of fistulas appear on the bluish red surface of the edematous skin

The lower lobes of the lung are frequently affected and the disease can suddenly become evident only when the pleura and chest wall are involved by direct extension from the lung Until then the patient may notice only fever, cough and expectoration Physical examination at this time reveals a diffuse tender indurated thoracic swelling with evidence of pulmonary consolidation Actinomycosis of the lower chest can extend through the diaphragm to produce subphrenic or hepatic abscess

Abdominal actinomycosis is often mistaken for appendicitis carcinoma of the cecum tuberculosis or amebiasis Patients with abdominal actinomycosis have been subjected to surgery for drainage of a supposed appendiceal abscess the true nature of the disease being recognized only when an indurated draining sinus remains and stubbornly refuses to heal Actinomycosis may also be mistaken for tumor of the reproductive organs in women or for tuberculous psoas abscess Peritonitis is rare

In the rare case of disseminated actinomycosis lesions appear in all parts of the body as a result of hematogenous spread A prominent feature is the presence of painful indurated nodules under the skin of the legs arms back and scalp

Diagnosis The disease is easily recognized by detecting *A bovis* in pus obtained from sinuses empyema fluid or abscess cavities Interpretation of the finding of *Actinomyces* in sputum is difficult of course because the organisms are normal inhabitants of the mouth Sulfur granules vary in size from several microns to 3 mm in diameter Large granules are nearly always found if a thor

peculiar to *C neoformans* Biopsied material should also be inoculated intraperitoneally in white mice *Cryptococcus neoformans* is highly pathogenic for these animals and readily demonstrated microscopically in sections or smears of their brains Serologic or skin tests are of no value in diagnosis

Treatment There is no dependable treatment Occasionally improvement has been reported after use of sulfadiazine Actidione cryptococcal vaccines and 2 hydroxystilbamidine but their value is hard to judge because of the tendency for cryptococcosis to undergo spontaneous remissions Surgical excision has often proved to be effective for cryptococcal masses in the skin bone lung or central nervous system

Because of the susceptibility of cryptococci to heat hyperthermia has been suggested as a form of treatment but has received little trial

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149 NORTH AMERICAN BLASTOMYCOSIS

Abraham I Braude

Definition North American blastomycosis is a fungous infection of the skin and viscera caused by *Blastomyces dermatiditis* It is one of the few systemic mycoses amenable to specific chemotherapy

Etiology In infected tissues *B dermatiditis* has the appearance of a yeast forming single buds from 3 to 24 μ in diameter Two features aid in recognition (1) its thick wall spoken of as "double contoured" because the inner and outer margins can be seen and (2) the wide opening between parent cell and bud at the base of attachment

In culture the fungus is dimorphic and appears as the wrinkled waxy yeast form on blood agar incubated at 37 C or as a mold with branching hyphae on Sabouraud agar at room temperature On microscopic examination the cultured yeast may be identical with that in the infected lesions or may have abortive mycelia The mycelia give rise to oval or pear shaped exogenous spores known as *conidia*

Although mice inoculated with *B dermatiditis* sometimes develop infections its virulence for laboratory animals is generally low

Pathogenesis and Pathology The skin has been proposed as a portal of entry of the fungus because of the prominence of cutaneous lesions and because infections have followed injury to the skin The lung is also a likely portal through which the fungus could gain entry in dust but it has never been cultured from the soil During the epidemic in Grifton N C in 1954 (Smith Harris Conant and Smith) all patients had pulmonary disease and only one had a blastomycotic lesion of the skin yet a respiratory mode of transmission could not be established

The characteristic pathologic features are found in the lung and skin Pulmonary lesions consist of focal granulomas or diffuse purulent pneumonia and vary in size from miliary nodules to confluent areas involving an entire lobe The granulomas can undergo caseation and fibrosis *Blastomyces dermatiditis* is often found within giant cells or other phagocytes facilitating differentiation from tuberculosis

The characteristic cutaneous lesion consists of microabscesses just beneath the epidermis surrounded by a granulomatous reaction The epidermis itself often becomes so hyperplastic that it resembles an epithelioma

Dissemination of the infection to the brain bones urogenital tract liver spleen and lymph nodes can occur

Clinical Manifestations In the typical case of systemic blastomycosis the onset is insidious The patient may seek medical attention because of a persistent "chest cold" low grade fever weight loss or progressive disability Physical examination and roentgenogram of the chest disclose evidence of pneumonia which can involve any segment or lobe of the lung Cavitation is frequent and mediastinal lymph nodes may be prominently enlarged Hemoptysis purulent sputum chest pain and dyspnea appear as the disease progresses Although the pulmonary infection can subside spontaneously extrapulmonary lesions of the skin *bones joints* and viscera eventually call attention to dissemination of the infection in many patients These metastatic suppurative lesions are accompanied by an increase in fever sweats chills and weakness Death in the untreated infection sometimes occurs less than 6 months after the onset but most patients live for a year or two The over all mortality rate in the systemic form of blastomycosis is said to be 92 per cent in patients who have been fol

brownish slimy appearance Unlike other pathogenic yeastlike fungi cryptococci never form mycelia regardless of temperature of incubation or culture medium Most cells of *C neoformans* are killed in 24 hr at temperatures of 40 6 C or higher

Pathogenesis and Pathology Cryptococci resembling *C neoformans* have been isolated from soil bird droppings the surface of fruit and from the skin and intestinal tract of normal man Hence *it is possible for infections to be either of endogenous or exogenous origin* Whatever the mode of entry may be the organism ultimately finds its way to the nervous system in most cases of cryptococcosis Although the neurologic disturbances overshadow those produced elsewhere there is good evidence that foci of infection are usually established in the lung and other viscera before dissemination to the brain and the meninges occurs Often the pulmonary foci give rise to no clinical findings although they can be detected if a careful search is made at postmortem examination

Penetration of tissues by the cryptococcus does not evoke the active inflammatory response observed with other fungi or bacteria The cellular reaction is very slow to develop and is seldom intense *The cryptococcus seems to meet little* resistance in the body and frequently proliferates so freely that macroscopic masses of gelatinous yeasts fill the lesions Older lesions occasionally show granulomatous reactions The small number of cryptococci observed within such exudates suggests that they are capable of destroying the organism This may account in part for the clinical fact that lymphomatous diseases involving the mononuclear cells lower resistance to cryptococcal infection At other times however many cryptococci are present within mononuclear and giant cells It is unusual to see necrosis of the host tissue in cryptococcosis

Granulomas or gelatinous cryptococcal masses can appear in the nervous system lungs bones or skin *In the nervous system lesions usually develop* in the meninges at the base of the brain with resulting involvement of the brain stem cranial nerves and cerebellum Large masses of yeast may accumulate in the subarachnoid space and extend diffusely along the perivascular spaces into the brain substance to produce cystic nodules Because the fungal masses shrink after fixation of the brain in formalin cystlike spaces remain These spaces were thought to result from a histolytic action of the fungus by early observers who named the yeast *Torula histolytica* In the lung the disease may be scattered diffusely in the form of miliary nodules or solitary granulomas easily mistaken for pulmonary neoplasms may occur Pulmonary cavitation or hilar lymphadenopathy is extremely rare These characteristics of the cryptococcal pulmonary lesion are helpful in distinguishing the disease from tuberculosis sarcoidosis and other mycoses

Clinical Manifestations Most patients with cryptococcal infection come under the care of a physician after the onset of neurologic manifestations Complaints of severe headache diplopia dizziness ataxia vomiting tinnitus memory disturbances or Jacksonian convulsions are common Fever is usually low and can be absent Many patients die within a few months but some have lived for many years as the disease undergoes remissions and relapses

When pulmonary infection is present in the absence of meningoencephalitis the patient is generally *free of constitutional symptoms The disease* is detected when roentgenographic examination of the chest shows a dense *solitary* infiltration of the lower portions of the lung

Involvement of bones in the absence of disseminated disease is rare and cryptococcosis of joints is almost always secondary to adjacent osseous lesions

Disseminated infection can also lead to skin lesions which take the form of multiple nodules of papules which vary from a few millimeters in diameter to masses resembling strawberries in size and color

In every patient with cryptococcosis the possibility of an underlying disorder such as Hodgkin s disease lymphosarcoma or leukemia should be considered

Diagnosis Cryptococcal meningitis must be distinguished from other diseases which present the syndrome of aseptic meningitis (p 1071) such as brain abscess tuberculous meningitis and coccidioidal meningitis In each of these the spinal fluid is sterile by ordinary cultural methods and may contain from a few to several hundred mononuclear cells an increased amount of protein and a reduced concentration of glucose Because *C neoformans* is recovered with much greater ease *than the etiologic agents* of the other diseases culture of the spinal fluid is the decisive procedure in differential diagnosis The cryptococcus is isolated on Sabouraud s agar at room temperature and can usually be recognized after 1 to 2 weeks In tuberculous and coccidioidal meningitis positive cultures are much fewer and in uncomplicated brain abscess the spinal fluid is sterile Cryptococcal cells may also be found by direct microscopic examination of sediment from centrifuged spinal fluid Mixing a drop of sediment with India ink on a glass slide facilitates the recognition of the mucinous capsule The organism can also be seen in tissue removed by biopsy Intracellular forms with small capsules can resemble *Histoplasma capsulatum* but may be differentiated by mucicarmine which stains the capsular mucopolysaccharide

personnel The mycelium and its spores are pathogenic for various laboratory animals The mycelial form is converted to a thick walled spherule filled with endospores in animal tissues

Pathogenesis and Pathology Coccidioidomycosis is acquired by inhalation of *chlamydospores* in endemic areas in the semiarid regions of the Southwestern United States and the Chaco district of Argentina The majority of infections occur during the dry seasons particularly after exposure to dust storms The fungus is thought to grow in the soil in rainy weather and become disseminated in dust during dry weather This concept is supported by isolations of C immitis from soil and from desert rodents These animals are thought to be a reservoir for contamination of soil

The inhaled spores are carried to the terminal bronchioles and alveoli where the first reaction is an outpouring of polymorphonuclear leukocytes fluid and a few mononuclear cell In most cases the organism is probably killed or at least arrested at a stage when the lesion is too small to be detected by clinical means In others the organisms proliferate and elicit a varying inflammatory response which appears to depend on the rate of multiplication of the fungus The phase of rapid multiplication as manifested by frequent discharge of endospores from the ripened spherules elicits suppuration and an exudate rich in polymorphonuclear leukocytes The phase of slow multiplication with infrequent rupture of spherules produces a granulomatous reaction in which epithelioid cells and giant cells predominate Although polymorphonuclear leukocytes congregate about the point of rupture of a spherule and actually invade the broken capsule attempts at phagocytosis by these cell are unsuccessful As the released endospores develop into spherules the neutrophilic reaction gives way to proliferating mononuclear cells which often are able to ingest the fungus

Either phase of this inflammatory cycle may predominate or a mixture of the two may be found Rapidly progressive infections produce large areas of confluent suppurative pneumonia and necrosis of adjacent bronchi In contrast granulomatous lesions contain exudates composed almost exclusively of mononuclear cells and giant cells which fill the alveoli but leave their walls intact Both reactions are accompanied by involvement of the overlying pleura and of the hilar and mediastinal lymph nodes Ultimately the bronchopneumonia in most patients resolves or heals by fibrosis in others the lesions are permanently arrested but persist as cavities or solid nodules

Recovery is accompanied by the development of hypersensitivity to the fungus This hypersensitivity is apparently responsible for at least two special pathologic manifestations (1) *erythema nodosum* this is a sterile focal nodular granulomatous reaction usually limited to the skin of the lower extremities and characterized by extravasation of red cells into the lesion (p 1710) (2) *pleural effusion* It is believed that rupture of a pleural granuloma discharges antigenic material onto the sensitized pleural membranes

In patients who do not develop dermal hypersensitivity the infection spreads systemically to involve lymph nodes spleen bones liver kidney meninges skin adrenals and pericardium In the meninges the two inflammatory reactions can take special forms (1) the granulomatous reaction is commoner and produces a firm plastic lesion which encloses the brain stem and other structures in a rigid mass of tissue (2) the suppurative reaction results in outpouring of polymorphonuclear leukocytes with little granulomatous change In either type but especially in the granulomatous the involvement of the brain stem can lead to severe hydrocephalus

Clinical Manifestations The infection may be either benign or disseminated The benign infection so-called "desert fever" is self limited As many as 50 per cent of benign infections are asymptomatic The remainder are accompanied by symptoms like those of influenza or pneumonia After an incubation period of 1 to 3 weeks the patient experiences fever chills fatigue headache and symptoms of respiratory infection The most frequent complaint is poorly localized chest pain aggravated by breathing or coughing Some patients also experience substernal pain on swallowing of sufficient severity to prevent eating solid food A nonproductive cough is common but hemoptysis is infrequent Physical findings are scant except in those patients (3 to 20 per cent) who develop erythema nodosum or pleural effusion Although hydrothorax may be massive and require repeated thoracenteses it eventually resorbs without further difficulty

Despite the paucity of signs in the chest prominent abnormalities are found in roentgenograms These include focal areas of pneumonic infiltration hilar and mediastinal lymphadenopathy pulmonary nodules or cavities and pleural effusion The commonest are single or multiple infiltrations which may appear in any segment and can simulate secondary tuberculosis if the upper lobe is involved They usually resolve after several weeks

In about 2 per cent of benign infections a solid or cavitary pulmonary lesion remains after the active stage is over The typical cavity of coccidioidomycosis is peripheral has a thin wall and gives a cystlike appearance in roentgenograms Bronchoscopic examination may disclose stenosis and ulceration of the bronchus leading to the corresponding lobe This deep bronchial disease is responsible for

lowed for 2 years or longer without specific therapy

Primary infection of the skin (Gilchrist's disease) first appears on an unclothed area such as the hands face or forearm but not the scalp palms or soles The infection begins as a firm nodule surrounded soon by similar lesions which tend to coalesce Suppuration in the center of the nodule is followed by partial healing and fibrosis as extension occurs peripherally The hyperplasia of the epithelium gives these lesions a hard raised wartlike margin When fully developed blastomycosis of the skin presents the appearance of one or more ragged ulcers with partially healed centers and thick raised margins *The primary cutaneous infection may be* confined to the skin for months or years before it spreads to the viscera

Diagnosis Pulmonary blastomycosis closely resembles tuberculosis carcinoma of the lung aspiration pneumonitis and other fungous infections including coccidioidomycosis actinomycosis nocardiosis and histoplasmosis Differentiation must be based on the recovery of the etiologic agent because neither clinical nor epidemiologic features are specific Most cases of North American blastomycosis are found in the Southeastern United States and in the Mississippi River Valley but the disease occurs throughout the United States and Canada Occupational history sex race and age are of no diagnostic aid

It is usually possible to find *B dermatiditis* by *microscopic examination of biopsied material sputum* or pus The thick walled yeastlike form can be readily observed if a drop of purulent material is first mixed on a slide with a drop of 20 per cent potassium hydroxide and allowed to stand at room temperature for 30 min *B dermatiditis* is readily isolated by culturing pus on Sabouraud agar at room temperature and on blood agar at 37 C Inoculation of mice or other animals is usually not a successful method for recovering the fungus

The value of the skin test for blastomycosis using killed cells or blastomycin is limited because of negative reactions in patients with disseminated infection and cross reactions in persons with hypersensitivity to coccidioidin or histoplasmin The complement fixation test is positive in high titer with sera of patients who have systemic infections The results of intradermal and serologic tests may be of prognostic value Patients with marked dermal hypersensitivity and low serum titers of complement fixing antibody are said to have a better prognosis than those with negative skin tests and high complement fixation titers Neutrophilic leukocytosis and hypochromic anemia are usually present in systemic blastomycosis

Treatment The outlook in blastomycosis has been greatly improved by the use of stilbamidine or 2 hydroxystilbamidine Either drug is given daily or every other day by slow intravenous drip in increasing doses up to 250 mg A total of 5 to 8 Gm is usually required for control of the disease Two untoward reactions have been observed with stilbamidine One of these is an unavoidable anesthesia over the distribution of the trigeminal nerve it appears several months after injection of the drug and lasts for at least 2 years Unless the drug is shielded from light it deteriorates rapidly and the breakdown products can cause hepatic and renal injury 2 Hydroxystilbamidine is less likely to produce neuropathy and has the additional advantage of being stable to light A diet low in proteins and purine has been advocated during treatment because these substances antagonize the action of the stilbamidines Although these agents disappear immediately from the circulation after intravenous *injection they accumulate in the tissues and persist* there for as long as a year Surgical excision of pulmonary cavities or destroyed tissues is sometimes required in addition to chemotherapy

Iodides and vaccines no longer hold an important place in the treatment of blastomycosis

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150 COCCIDIOIDOMYCOSIS

Abraham I Braude

Definition Coccidioidomycosis is an infection acquired by inhalation of *Coccidioides immitis* a fungus existing only in the mycelial phase in nature and converted to a spherule in tissues Although most infections are mild or unapparent *C immitis* may produce a fatal disseminated disease with destructive lesions in the lungs lymph nodes spleen liver bones kidneys and brain

Etiology Unlike other dimorphic pathogenic fungi *C immitis* can be cultured only in the mycelial phase It grows *readily at room temperature* or at 35 C and produces white cottony mycelia As a culture ages the segmented mycelium breaks up into thick coated rectangular *arthrospores* 2 by 4 μ in size These arthrospores can survive in stored cultures and are highly infectious for laboratory

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151 HISTOPLASMOSIS

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Definition Histoplasmosis is a protean infection caused by the dimorphic fungus *Histoplasma capsulatum* an organism characteristically found as a tiny body within reticuloendothelial cells The disease varies from mild or unnoticed respiratory infection to widely disseminated lethal disease characterized by fever anemia hepatomegaly splenomegaly leukopenia pulmonary lesions ulcerations of the gastrointestinal tract and adrenal necrosis

Etiology Although *H capsulatum* grows on Sabouraud agar at room temperature as a spore bearing mold it is transformed immediately upon animal inoculation into nonencapsulated oval yeast like cells measuring 2 by 4 μ In histologic section the protoplasm is shrunken so that the unstained space beneath the cell wall has the appearance of a capsule The name *capsulatum* is based on a misinterpretation of the nature of this unstained space The fungus also grows in the yeastlike phase if incubated at 37 C in sealed tubes of blood agar The most distinctive cultural feature however is the tuberculate *chlamydospore* found only on mycelia it is round 10 by 20 μ in diameter and covered with warty projections Another smaller spore not distinguishable from that of *Blastomyces dermatiditis* is also present on the mycelium

Pathology and Pathogenesis The source of human infection is probably soil containing spores of *Histoplasma* Several studies have emphasized the isolation of the fungus from soil in areas inhabited by chickens but conclusive evidence connecting human infection with a definite animal reservoir is still lacking In most cases the portal of entry is probably the lung but the gastrointestinal tract must also be considered in patients whose initial lesions are in the mouth and pharynx

The basic pathologic process is the multiplication of *H capsulatum* in cells of the reticuloendothelial system The yeast form multiplies extensively and greatly distends the cells Proliferating histiocytes encroach on parenchymal cells and this leads to enlargement of the infected organ The liver lymph nodes lung spleen adrenal bowel and marrow may be affected by this diffuse reticuloendothelial disturbance in disseminated histoplasmosis

In addition to the diffuse lesions of the reticuloendothelial system the tissues contain lesions consisting of nodular accumulations of epithelioid cells and giant cells of the Langhans type The non *caseous granuloma probably represents an effective* defensive action and histoplasma organisms are difficult to demonstrate in the epithelioid cells of such a lesion

Caseous necrosis may accompany both types of lesion The adrenals which are involved in nearly all disseminated infections are often massively enlarged Caseous necrosis is usually present in the center of the pulmonary granulomas which resemble those of cavitary pulmonary tuberculosis Necrotizing histoplasmosis may also take the form of renal papillitis Extracellular forms of histoplasma are readily found in the necrotic areas of all organs by special stains (periodic acid–Schiff Gridley) These extracellular organisms may be much larger than the intracellular ones appear distorted and occasionally assume the mycelial form

Clinical Manifestations The signs and symptoms of histoplasmosis range from those of a slight self limited infection to the overwhelming disturbances of fatal disseminated disease The high incidence of positive intradermal reactions to histoplasmosis in healthy persons in many parts of the world indicates that most infections by *H capsulatum* are unapparent or very mild This variability in severity is observed among different persons involved in the same outbreak Severe infections are characterized by prolonged fever coma dyspnea chest pain weight loss prostration widespread pulmonary infiltrates hepatomegaly and splenomegaly Other infected persons may exhibit only a benign acute pneumonitis lasting a week or less while still others are entirely free of symptoms Widespread ill-defined noncalcified pulmonary infiltrates of miliary size or larger are found in symptomatic infections and may also be present although less extensively in the asymptomatic ones Eventually pulmonary lesions either disappear or calcify In the east central part of the United States there is a high incidence of pulmonary calcification in persons who have negative tuberculin and positive histoplasmin skin tests

Least resistance to histoplasmosis seems to be encountered in young infants and in adults after the fifth decade Most cases of disseminated infection have occurred at these extremes of life but with somewhat different clinical manifestations in the two groups In the infant there are fever emaciation anemia and leukopenia and evidence

the distention of the cavities Residual solid lesions can be as large as 3 cm in diameter Both solid and cavitary lesions are commoner in the upper lobes Calcification is rare

In a relatively few individuals (0 05 to 0 2 per cent) the primary infection progresses to the disseminated form of the disease Dissemination usually occurs within a few months of infection Dark skinned persons are more vulnerable to this type of spread and experience a higher death rate Among Negroes and Filipinos 85 to 90 per cent with dissemination succumb as compared to 50 per cent of whites Patients who develop progressive coccidioidomycosis do not give a history of erythema nodosum

The course of disseminated infection is marked by the appearance of fungating or ulcerating skin lesions multiple pulmonary nodules or cavities widespread destructive lymphadenopathy osteomyelitis and meningitis Weight loss fever and weakness are the outstanding systemic manifestations and the course is often rapid with death occurring in less than a year If vital organs are spared however patients with disseminated coccidioidomycosis may feel surprisingly well continue to work and even gain weight despite the presence of large numbers of *C immitis* in the sputum or subcutaneous abscesses The meningeal form is invariably fatal but even this is compatible with survival for several years In the presence of meningitis with progressive hydrocephalus patients experience severe headaches cranial nerve palsies memory disturbances and disorientation The spinal fluid shows 100 to 200 cells mostly mononuclear elevated protein and frequently a reduction in glucose concentration

Diagnosis With the exception of meningitis *C immitis* is easily recovered from the lesions of disseminated coccidioidomycosis by direct examination and cultures of exudates or biopsied tissues The characteristic spherule with endospores is best seen in purulent material treated with 20 per cent potassium hydroxide Occasionally in biopsied tissue spherules may all be immature and contain no endospores making them indistinguishable from *Blastomyces dermatiditis* Cultural identification becomes essential for diagnosis On Sabouraud agar mycelial growth appears in 4 to 8 days and inoculation of mice produces multiple necrotic lesions containing spherules In meningitis only a few spherules appear in the spinal fluid despite the presence of large numbers in the granulomatous exudate around the brain stem Occasionally the culture of 20 to 30 ml of spinal fluid yields positive results but sometimes the diagnosis can only be based on serologic tests

Serologic tests are performed with coccidioidin a filtrate from cultures of *C immitis* By the third week of primary infection precipitins are found in the serum of 91 per cent of patients with symptomatic infection but in only 7 per cent of asymptomatic individuals Complement fixing antibodies appear later and persist longer than precipitins in nondisseminated coccidioidomycosis they are almost always present in the disseminated disease Intradermal tests with coccidioidin are of value in the recognition of primary benign infections because they become positive before the precipitins appear but in disseminated infection the skin test is frequently negative

The roentgenographic appearance of pulmonary lesions is suggestive of primary coccidioidomycosis if hilar lymphadenopathy progresses while the parenchymal infiltrate is subsiding or if the adenopathy is associated with multiple areas of pneumonitis A residual smooth thin walled cavity without surrounding parenchymal infiltration is also characteristic of the primary form of the disease Other residual lesions include calcified or noncalcified nodular foci and localized bronchiectasis In disseminated pulmonary infection the commonest picture is that of multiple infiltrations accompanied by pleural involvement and prominent hilar or mediastinal lymphadenopathy

The only remarkable hematologic finding is eosinophilia which may reach 35 per cent of the total leukocyte count in the primary disease

Treatment Scattered reports suggest that Actidione prodigiosin and the stilbamidines may be of value in an occasional patient but chemotherapy is usually ineffective in disseminated coccidioidomycosis Variations in results of therapy may be related to differences in sensitivity among strains of the fungus or to differences in the degree of endosporulation Large numbers of endospores packed within spherules are presumably sheltered more from the antifungal drugs than single immature spores

Primary surgical excision of residual pulmonary foci is indicated if these lesions become troublesome because of secondary infection or hemoptysis Dissemination of the disease from these foci almost never occurs

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152 OTHER FUNGOUS INFECTIONS

Abraham I Braude

SPOROTRICHOSIS

Definition Sporotrichosis is a chronic infection due to *Sporotrichum schenckii* It is characterized by the formation of suppurating nodules along the lymphatics of the skin and subcutaneous tissues Hematogenous dissemination is rare

Etiology The fungus *S schenckii* exhibits the dimorphism On Sabouraud agar at room temperature its growth is mycelial but in the tissue it takes the form of tiny cigar shaped yeast cells The yeast phase can be produced in vitro by incubation at 37 C on blood agar containing cystine

Pathogenesis and Pathology The fungus lives as a saprophyte on vegetation and penetrates the hands when the skin is broken Many cases have followed injury by thorns and an outbreak of sporotrichosis occurred among South African natives exposed to *S schenckii* growing on timbers supporting a gold mine

After penetrating the skin the fungus spreads up the extremities and evokes nodular lesions along the thickened lymphatics Microscopically the nodules are granulomas with central necrosis In exceedingly rare infections the organism may become disseminated throughout the subcutaneous tissues the liver testicles bone and kidney Disseminated disease is not usually accompanied by primary infections of the extremities and its portal of entry therefore is believed to be the mucosa of the gastrointestinal tract

Clinical Manifestations There is a marked disproportion between symptoms and findings A chain of hard reddened discrete lumps extends up the arm or leg to the axilla or groin and the intervening lymphatics are red and thickened but there is no pain fever or other constitutional symptoms Older nodules often rupture to produce fistulas or ulcers In the rare patient with disseminated sporotrichosis constitutional symptoms may be marked and the disease rapidly fatal Unlike other disseminated mycoses sporotrichosis almost never involves the lungs or central nervous system

Without treatment sporotrichosis does not heal and the lesions persist often with secondary bacterial infections

Diagnosis The fungus cannot be seen upon microscopic examination of biopsied material or pus in most cases Cultural isolation is invariably successful however if pus is aspirated from an unbroken nodule and inoculated onto Sabouraud agar The growth at first has the soft creamy character of bacterial colonies and later develops a wrinkled dark brown appearance without the cottonlike filament of most molds Microscopically typical clusters of pear shaped spores are found at the tips of conidiophores arising from the tangled mass of delicate branched mycelia If the mold or the pus itself is inoculated intraperitoneally into mice or rats numerous yeast forms will be seen in lesions of the peritoneal cavity or testicle in which they take the form of gram positive cigar shaped rods within polymorphonuclear leukocytes

Recovery of the organism by these techniques permits ready differentiation of sporotrichosis from other chronic infections of the subcutaneous tissues such as syphilis tularemia blastomycosis coccidioidomycosis and tuberculosis (see p 907) The hard sporotrichotic lesions are sometimes mistaken for syphilitic gummas and their response to iodides is interpreted as therapeutic proof of the diagnosis

Treatment Both forms of sporotrichosis are almost *invariably dramatically cured by saturated* potassium iodide This should be given orally in starting doses of 10 drops t i d after meals and gradually increased to the point of maximum tolerance Treatment should be continued for a month after lesions disappear Additional local therapy may be required for cutaneous ulcers which should be painted with tincture of iodine It may also be necessary to excise the epidermal lesions as these do not usually subside with oral iodides

MONILIASIS (Candidiasis)

Definition *Moniliasis is a common mild mucocutaneous* infection due to *Candida albicans* This fungus is also an unusual cause of widespread visceral infection

Etiology Among the many species of *Candida* only *C albicans* is pathogenic for man On the usual nutrient laboratory media *C albicans* grows almost exclusively as a budding yeast in creamy white colonies but produces both mycelia and yeastlike cells in infected tissues

Pathogenesis *Candida albicans* resides normally on the mucous membranes and is frequently cultured from the mouth and feces of persons in good health The rate of cultural isolation from feces in numerous surveys has ranged from 14 to 19 per cent In debilitated infants and sometimes in adults the fungus may produce white patches on the buccal mucosa and initiate mild inflammation reaction in the underlying tissues In pregnancy and diabetes *C albicans* frequently establishes a mild superficial infection of the vagina Presumably the high glycogen content of the vaginal mucosa in pregnancy and the glycosuria of diabetes favor its growth *Candida* multiplies excessively in the bowel or mouth if the normal bacterial flora are suppressed by chemotherapy Although true infection seldom accompanies this overgrowth of *Candida* the large

of widespread involvement of many viscera including the liver spleen lung bowel lymph nodes adrenals skin kidney brain eye or endocardium While the same degree of dissemination may occasionally occur in the adult usually the visceral involvement is less widespread Unlike the disease in infancy adult histoplasmosis shows a marked predilection for males Histoplasmosis of the lips mouth nose and larynx occurs almost exclusively in adults and is the initial manifestation in about one third of the fatal cases Among the various syndromes encountered are subacute vegetative endocarditis massive lymphadenopathy resembling tuberculosis or lymphoma various forms of pneumonia including an interstitial type with capillary alveolar block and meningitis The last is characterized by signs of basilar localization with spinal fluid findings and a clinical course identical with those of tuberculous meningitis

In addition to the acute benign and disseminated infections chronic localized histoplasmosis occurs in adults Although frequently accompanied by necrosis or ulceration this form is basically a granuloma and its tendency to remain localized is probably related to the effective defensive activity of the granulomatous reaction

Two main clinical types are encountered (1) *Pulmonary* This may resemble pulmonary tuberculosis in all respects The patient can be asymptomatic or complain of a chronic and occasionally productive cough Roentgenograms will show lesions identical with those of reinfection tuberculosis sometimes with cavitation and accompanied by consistently positive cultures of sputum for *H capsulatum* (2) *Mucocutaneous* Ulcers of the mouth tongue pharynx gums larynx penis or bladder are rare lesions found only in adults Regional lymphadenopathy is common in these types

Diagnosis Isolation of *H capsulatum* is not difficult in disseminated or chronic localized infections if cultures are made of bone marrow blood biopsied lesions sputum or exudate from an ulcer After incubation of infected material on Sabouraud agar at room temperature there appears a white cottony colony which later turns brown and produces the diagnostic tuberculate chlamydospores Material may also be cultured at 37 C on Francis medium or blood agar but the growth is yeastlike and the diagnostic spores are not found Isolation from sputum is best accomplished in mice because contaminants are suppressed and the mouse is extremely susceptible to infection by *Histoplasma* The animal does not die but subculture of the spleen one month later on Sabouraud agar yields the organism *Histoplasma* may also be seen in bone marrow material from open or biopsied lesions and occasionally in blood smears of terminally ill patients Special fungus stains (periodic acid-Schiff Gridley) should be used Certain intracellular forms of *Cryptococcus neoformans* may be indistinguishable from *Histoplasma* in histologic sections unless stains for the cryptococcal mucinous capsule are employed

In those cases from which *H capsulatum* cannot be isolated indirect clues to identification are (1) history of exposure to soil or dust in an endemic area (2) positive complement fixation tests (3) positive histoplasmin skin tests and (4) development of miliary calcifications in the lung Although these criteria are not dependable individually they appear to be reliable when used together The serologic and skin tests are frequently negative in culturally proven cases of histoplasmosis and their specificity is not fully established

Histoplasmosis must be differentiated from tuberculosis sarcoid leukemia infectious mononucleosis Hodgkin s disease brucellosis and kala azar Because cortisone is frequently of value in sarcoid but can cause dissemination in histoplasmosis differential diagnosis between these two diseases is critical Biopsied tissue in both diseases contains morphologically identical granulomas For this reason the diagnosis of sarcoid should be withheld until tissues have been examined with special fungus stains In kala azar the intracellular Leishman Donovan body bears a close resemblance to *H capsulatum* and cultural isolation of the fungus may be important in distinguishing between the two

Treatment The only dependable treatment is excision of localized lesions Chemotherapy of disseminated histoplasmosis has been disappointing despite the use of many different agents including sulfonamides antibiotics and iodides Occasionally questionable benefit has been observed with stilbamidine and ethyl vanillate but these drugs are usually ineffective

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instances there is direct extension along lymphatic pathways Death can occur from secondary bacterial infection

Diagnosis The characteristic granules are 0 5 to 2 mm in diameter and may be white yellow black or red Nocardial granules are easily distinguished from those of *A boydii* and other higher fungi by direct microscopic examination They are masses of radiating gram positive filaments those of higher fungi contain large segmented hyphae and numerous chlamydospores Inoculation of either type of granule on Sabouraud agar is followed rapidly by characteristic growth

Roentgenograms of the foot disclose destruction of bone which is more extensive than the external appearance and pain might indicate

Treatment Wide excision of infected tissues may slow the progress of the disease and antibacterial chemotherapy is valuable in arresting secondary infection There is no known cure however and most cases eventually require amputation of the foot

CHROMOBLASTOMYCOSIS

Definition Chromoblastomycosis is an infection of the skin produced by several species of the genus *Phialophora* and characterized by slowly progressive cauliflowerlike lesions of the legs of agricultural workers in tropical or subtropical regions

Etiology The three species *P pedrosi P compactum* and *P verrucosa* cannot be distinguished upon microscopic examination of infected tissue in which all appear as small clusters of spores with thick dark brown walls On culture however the three differ in their methods of sporulation The species most commonly found *P pedrosi* exhibits three types of spore formation (1) branching chains of spores borne at the tips of long conidiophores (2) clusters of spores forming sleeves about the hyphae and (3) balls of spores arising in the cuplike ends of very short flask shaped conidiophores *Phialophora verrucosa* forms only the third type of spore and *P compactum* is recognized by chains of spores arranged in compact masses On Sabouraud agar all three grow very slowly and will produce deeply pigmented olive or black colonies

Pathogenesis and Pathology The fungi undoubtedly live in the soil or vegetation and enter the skin of agricultural workers

Three pathologic processes are found (1) microabscesses in the dermis containing numerous fungi (2) extensive fibrosis and (3) epidermal hyperplasia and hyperkeratosis The lesions progress along the lymphatics but not beyond them dissemination through the blood or deep penetration into bone does not occur

Clinical Manifestations The earliest lesion is a papule which develops into a well circumscribed bluish lesion with a warty raised margin Although it resembles the cutaneous form of North American blastomycosis at this early stage it does not spread peripherally Instead adjacent new lesions appear over a period of years and as the epithelial hyperplasia and hyperkeratosis increase the entire area assumes a cauliflowerlike appearance Eventually the whole extremity is covered Pain and constitutional symptoms are absent unless secondary bacterial infection occurs or elephantiasis develops as a result of lymphatic scarring

Diagnosis The typical dark brown septate bodies are seen in large numbers in biopsied tissue or pus and brown hyphae can be found in crusts treated with 10 per cent potassium hydroxide For specific identification however it is necessary to culture the slowly growing fungus on Sabouraud agar

Treatment Early in the disease the lesions may be destroyed by electrocoagulation or removed by surgical excision Later in the course excision of the larger nodules leaves indolent ulcers which heal very slowly

Except for treatment of secondary infection there is no specific medical therapy The disease is never fatal however and the usefulness of the limb is retained despite its unsightly appearance

SOUTH AMERICAN BLASTOMYCOSIS

Definition South American blastomycosis is a highly destructive but curable infection that results from invasion of the nasopharynx by *Blastomyces brasiliensis* It occurs only in South America From the pharynx the disease can extend locally to regional nodes or spread to the lungs and abdominal viscera

Etiology Multiple buds on the yeastlike cell of *B brasiliensis* distinguish it morphologically from its North American counterpart *B dermatitidis* The tiny multiple buds have the appearance of a crown of small beads attached to the cell wall The fungus reproduces by budding both in tissues and when cultured at 37 C At room temperature it produces mycelia which bear spores resembling those of *B dermatitidis*

Pathogenesis In most cases the portal of entry of this exogenous fungus is the nasopharynx Here it produces a destructive lesion with gross swelling and ulceration and eventual extension to the cervical lymph nodes Occasionally the primary lesion is inconspicuous and massive enlargement and suppurative necrosis of the regional lymph nodes are the predominant pathologic changes Hematogenous spread to other lymph nodes liver spleen and bone eventually leads to suppurative or granulomatous nodules in those organs In addition to the naso-

inoculum provides a threat in debilitated persons who may develop aspiration pneumonia or even *Candida* septicemia Visceral infection can take the form of vegetative endocarditis brain abscess meningitis or pyelonephritis The visceral lesions are granulomatous nodules or abscesses containing both mycelia and yeastlike cells

Clinical Manifestations No systemic disturbances accompany the local signs of mucocutaneous infection Infection of the mucous membranes known as *thrush* gives rise only to soft white patches on the tonsils cheeks gums and tongue These patches are easily removed and leave a reddened surface Although usually self limited the disease may become chronic and spread to other mucosal surfaces or intertriginous areas in the groins the antecubital fossae the interdigital folds the inframammary areas the umbilicus and the axillae Eczematoid lesions and vesicles are also found in vulvovaginal moniliasis of pregnancy or diabetes

Aspiration pneumonia is probably the chief form of visceral moniliasis It is seen in debilitated persons often in the course of intensive therapy with tetracycline or other antibiotics and may be accompanied by mixed infection with bacteria Cough chest pain and high fever are prominent Less extensive involvements of the lung are said to heal completely or progress to chronic infections but the disease is sometimes fatal

Septicemic infections are seen in the late stages of severe debilitating disease and seem to occur most commonly in children receiving intensive antibiotic therapy The chief clinical manifestation is fever Septicemic moniliasis also accompanies vegetative endocarditis a disease that has been described mainly in narcotic addicts Meningitis is *another rare form of moniliasis it produces a* clinical syndrome similar to tuberculous meningitis

Diagnosis In thrush the organisms are seen upon microscopic examination of the white patches as a tangled mass of mycelia and yeastlike cells They grow readily on Sabouraud agar In septicemias the fungus can be isolated repeatedly from the blood Pulmonary moniliasis may be difficult to recognize because *C albicans* is a normal resident of the oropharynx and may appear in the sputum in the absence of respiratory infection For this reason it is often impossible to be certain of the diagnosis of pulmonary moniliasis unless the organism is demonstrated in pulmonary lesions at autopsy or surgery

Treatment Thrush and vaginal moniliasis are best treated by nystatin administered orally in *doses of 500 000 units t i d Topical therapy with* nystatin ointments or with alcoholic solutions of gentian violet is effective in cutaneous moniliasis Nystatin may also be of some benefit in preventing candidal pneumonia or septicemia in debilitated persons whose mouth and intestines have become overgrown with *Candida* during treatment with antibiotics The value of the parenteral form of nystatin in systemic moniliasis is uncertain

MADUROMYCOSIS (Madura Foot)

Definition Maduromycosis is a chronic destructive infection of the foot characterized by the presence of *multiple fistulas which extrude mycotic* granules The term *maduromycosis* is used here synonomously with *mycetoma* and includes not only infections caused by *Nocardia* but also those caused by higher fungi with larger hyphae

Etiology The most frequent cause of maduromycosis in the United States is a higher fungus known as *Monosporium apiospermum* the "imperfect" form of the ascomycete *Allescheria boydii* The fungus grows rapidly on Sabouraud agar as a cottony mycelium containing asexual spores borne singly or in small groups at the tips or sides of conidiophores Other higher fungi which have been isolated in maduromycosis include members of such diverse genera as *Aspergillus Penicillium Madurella Cephalosporium* and *Phialophora*

Members of the genus *Nocardia* are important causes of Madura foot outside the United States *Nocardia madurae* is found in southeastern Asia and *Nocardia brasilinesis* in South America

Pathogenesis and Pathology The fungi *A boydii N madurae* and the others listed as infectious agents in mycetoma are inhabitants of the soil and enter the tissues of the bare foot It is presumed that the fungus is introduced by trauma In rare instances the hand may also be infected

The infection begins in the outer tissues and burrows *throughout the foot to destroy bone* muscle and connective tissue indiscriminately The areas of destruction show chronic suppuration with fibrosis and are connected by multiple fistulae which rupture to the outside Mycotic granules are seen in the suppurative foci The prolonged proliferation of granulation and scar tissue leads to enlargement of the affected part

Clinical Manifestations The earliest sign is usually a small swelling on the sole or dorsum of the foot This undergoes a recurring cycle of swelling suppuration and healing Later similar lesions appear on other parts of the foot and over a period of months the destruction of deeper tissues is manifested by slight or moderate pain generalized swelling and redness The course is intermittently progressive and there may be periods of remission *Ultimately however* the foot becomes a swollen deformed mass of destroyed tissue with many fistulous openings through which mycotic granules are discharged The infection does not become disseminated to other parts of the body but in rare

guinea pigs inoculated intraperitoneally and the recovery of *N asteroides* from miliary nodules in the omentum death occurs in less than a week from pathogenic strains (4) gram positive staining reaction

Pathogenesis *Nocardia asteroides* can be recovered readily from soil Nocardiosis appears therefore to be an exogenous infection usually having its portal of entry in the lungs In almost every patient with nocardiosis (other than maduromycosis) the earliest and most extensive lesions are pulmonary These lesions are accompanied by neither the intense fibrosis nor the typical granulomatous reaction found in pulmonary actinomycosis they are acute suppurative foci containing acid fast branching nocardial filaments A well defined wall is absent a fact which probably accounts for the marked tendency of nocardial abscesses to spread to the brain and to a lesser extent to the spleen skin peritoneum and kidney

Clinical Manifestations The chief symptom is cough usually productive of a thick sometimes bloody sputum Chest pain and dyspnea are common These symptoms are usually accompanied by fever sweats chills leukocytosis weakness anorexia and weight loss The illness may be prolonged and present the picture of a chronic pulmonary infection resembling tuberculosis lung abscess or unresolved suppurative pneumonia In nearly one third of the patients this syndrome is interrupted suddenly by the acute neurologic changes of metastatic brain abscess At this time the patient may experience severe headache and focal sensory or motor disturbance The protein cell and pressure of the spinal fluid are increased but the concentration of glucose is not reduced unless the meninges are also infected Metastatic infection of the skin is frequent and produces numerous scattered abscesses or single draining sinuses of the hand chest wall or buttocks

The disease usually progresses to a fatal outcome over a period varying from months to years

Diagnosis Because patients with nocardiosis are usually suspected of having tuberculosis their sputa are likely to be examined for tubercle bacilli The usual methods for concentrating tubercle bacilli often inactivate *N asteroides* however and the fungus will not be recovered after such treatment despite the readiness with which it otherwise grows on a variety of media *Nocardia asteroides* may also be overlooked in smears stained by the Ziehl Neelsen method because it is less resistant than the tubercle bacillus to the decolorizing action of acid alcohol If nocardiosis is suspected on clinical grounds precautions must be taken therefore against killing the organism by sputum concentration methods and against overdecolorizing it The first can be avoided by concentrating with trisodium phosphate the second by using a weak solution of acid alcohol

Although sulfur granules are not found in pulmonary or disseminated nocardiosis the gram positive filamentous organisms in nocardial exudates often resemble those found in infections due to *A bovis* The two pathogens can be distinguished however by the ease with which *N asteroides* is cultivated on Sabouraud or blood agar aerobically by its acid fast staining characteristics and by its pathogenicity for guinea pigs If biopsy material is available the nongranulomatous and minimally fibrotic character of the nocardial suppurative reaction also helps to distinguish it from that seen in infections due to *A bovis* The absence of tubercles of course is valuable in differential diagnosis from tuberculosis

The isolation of a few colonies of *Nocardia* from sputum or gastric juice however is by no means diagnostic of nocardial infection This organism is widely distributed as a saprophyte and only rarely achieves pathologic significance

Treatment The sulfonamide drugs especially sulfadiazine have been used successfully in the treatment of nocardiosis Penicillin and the tetracycline derivatives appear to be ineffective although the number of cases treated have been too few for definite evaluation of these agents The apparent resistance of a patient with nocardiosis to the tetracyclines and penicillin may be used in distinguishing it from actinomycosis due to *A bovis* as well as other forms of pulmonary infection which respond to these antibiotics Patients with nocardiosis should receive 8 to 12 Gm sulfadiazine daily Despite the poor clinical results with penicillin and oxytetracycline in vitro tests are warranted to determine the sensitivity of each new strain of *N asteroides* to various antibiotics An antibiotic selected on this basis can be used to supplement the sulfonamides

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MADUROMYCOSIS

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pharynx primary lesions can occur in the lymphoid tissue of the cecal and appendiceal regions

Clinical Manifestations The first symptoms usually result from painful ulcers of the mouth or nose although loss of appetite abdominal pain vomiting and diarrhea may be the first complaints when ulceration begins in the gut In other cases massive lymphadenopathy precedes other manifestations In the usual infection however there is a progressive extension of lesions from the mouth and neighboring skin The lymph nodes undergo suppurative necrosis and sinuses rupture through the overlying skin The patient suffers from severe pain fever inability to eat and cachexia Depending on the rapidity of spread to the viscera bones and central nervous system the disease is fatal after periods ranging from a few months to 3 or more years if untreated

Diagnosis Microscopic examination of pus or tissue treated with 10 per cent potassium hydroxide will reveal the characteristic multiple budding cells of *B brasiliensis* in addition to cells with single buds The multiple budding cells are also found in cultures on blood agar incubated at 37 C but growth is very slow and more than a month may elapse before colonies appear

Treatment The infection responds dramatically to sulfonamide drugs Sulfadiazine or sulfamerazine in doses of 4 to 6 Gm daily has been used successfully in arresting or curing the disease

MUCORMYCOSIS

Definition Mucormycosis is a fatal infection of the cerebral blood vessels of diabetics due to an unidentified fungus assumed to be a member of the order Mucorales on the basis of its morphology in fixed tissues The disease is characterized by ophthalmoplegia and meningoencephalitis

Etiology The etiologic agent has never been cultured from the brain so that presumptive identification of the fungus has necessarily been based on the appearance of its mycelium in fixed tissue preparations Its mycelium is described as broad branching and aseptate with a diameter of 6 to 15 μ A fungus identified as *Rhizopus oryzae* a species of the order Mucorales was recovered from the ethmoid sinus of a fatal case The hyphae of this fungus in culture were identical in appearance with that in the brain Members of the order Mucorales are common saprophytic fungi in nature and grow readily on virtually any media Hence the failure of cultural isolation from the brain must be attributed to inadequate attempts rather than technical difficulties

Pathogenesis and Pathology The mold belongs to a group of common ubiquitous fungi which only rarely display evidences of pathogenicity Although a few instances of infection in nondiabetics have been described the most consistent syndrome is that resulting in patients with poorly controlled diabetes and acidosis The portal of entry appears to be the paranasal sinuses and from here the organism is thought to extend along the invaded vessels to the cerebrum and retroorbital tissues Thrombosis of arteries and veins leads to multiple infarcts throughout the brain inflammatory response to the hyphae is minimal

Clinical Manifestations Cerebral mucormycosis is characterized by three features (1) uncontrolled diabetes with acidosis (2) ophthalmoplegia and (3) signs of acute diffuse cerebrovascular disease When the patient is first seen drowsiness and semistupor are usually attributed to the metabolic disturbance but the cerebral manifestations persist and progress after the acidosis is corrected Headache and fever are prominent

In addition to complete internal and external ophthalmoplegia there may be edema of the eyelids and retina and signs of retinal vascular occlusion Nuchal rigidity and mild mononuclear pleocytosis in the spinal fluid have also been described

Diagnosis The syndrome is so characteristic that it can be recognized by its clinical features alone Antemortem confirmation of the diagnosis by isolation of the fungus has never been accomplished although cultures of spinal fluid have been attempted

Treatment There is no specific chemotherapy Treatment should be directed toward rapid correction of the hyperglycemia and acidosis with the hope that remission will occur in patients who have not suffered irreparable neurologic damage

NOCARDIOSIS

Definition Nocardiosis is an infection caused by an aerobic actinomycete The disease may appear in the form of a lung abscess and spread to the brain and elsewhere in the body or it may produce a chronic deforming granulomatous infection limited to the foot (Maduromycosis)

Etiology Pulmonary and disseminated nocardiosis usually result from infection with *Nocardia asteroides* This organism is characteristically acid fast and its bacillary form resembles the tubercle bacillus The following properties of *N asteroides* permit easy differentiation from the tubercle bacillus (1) rapid growth on Sabouraud medium or on 10 per cent blood agar with colonies appearing in 6 to 14 days at room temperature (2) the presence in exudates of long branched mycelia forms in addition to the bacillary forms (3) rapid killing of

ordinary antiseptics drying and heat It may resist cold temperatures however and can be frozen and stored for long periods without its virulence being affected The organism does not remain viable however in whole blood or plasma which has been stored at refrigerator temperature for more than 96 hr

Pathogenic forms of *T pallidum* have not been cultivated and passed serially on artificial media Strains of the organism which have been cultured are not virulent in animals and differ morphologically from pathogenic *T pallidum* Rabbits and monkeys can be experimentally infected with syphilis

Frequency Exact information is not available as to the total number of persons infected with syphilis in the United States (i e *prevalence*) or the number of new infections occurring each year (i e *incidence*) There seems little doubt however that both have decreased considerably during the period since 1947 In 1947 approximately 108 000 cases of primary and secondary syphilis were reported to the Public Health Service whereas in 1955 only 6 500 cases were reported This dramatic decline in the incidence of syphilis is largely the result of the development of rapid treatment methods mass blood testing and large scale epidemiologic measures carried out by state and Federal health departments Another factor which may be responsible for the decline in the incidence of syphilis is the widespread use of penicillin for other diseases As a result of the decrease in syphilis case rates many of the states abandoned their public health control measures There is no doubt however about the need for continuing intensive control programs

Pathogenesis Syphilis is usually transmitted by direct and intimate contact with moist infectious lesions of the skin and mucous membranes Sexual contact is by far the commonest means of infection but transfer of the disease by kissing or biting occasionally occurs Indirect transmission—i e by contaminated objects—is exceptional since the organisms quickly die if allowed to dry The disease can be spread by inoculation with infected blood as in transfusion syphilis Infection is transmitted to the fetus through the placenta *Treponema pallidum* is apparently capable of penetrating the intact mucous membrane but a small abrasion is probably required for inoculation to occur through the skin Once the spirochete has penetrated the epithelium it enters the lymphatics and can be demonstrated in the regional lymph nodes a few hours after experimental inoculation From the lymph nodes the organism spreads rapidly throughout the body by way of the blood stream This spirochetemia may occur several weeks before appearance of the primary lesion at the site of inoculation The early seeding of *T pallidum* in various tissues is the basis for many of the later manifestations of the disease

About 3 to 6 weeks after the organism has entered the body a primary lesion the *chancre* develops at the site of inoculation The chancre is usually a single ulceration of the skin or mucous membrane it heals spontaneously About 6 weeks after its appearance a generalized skin eruption known as *secondary syphilis* develops In this stage systemic manifestations are common The signs of secondary syphilis also disappear spontaneously

This sequence of events in early syphilis is variable Infection without noticeable lesions probably occurs in a high percentage of cases and many individuals with late syphilis are unable to recall either primary or secondary manifestations

Following healing of the primary and secondary manifestations the patient may show no outward signs of the infection (*latent syphilis*) Nevertheless chronic progressive inflammatory changes may be taking place in the visceral organs or in the cardiovascular or central nervous system Clinical evidence of cardiovascular syphilis or neurosyphilis may not develop for 10 to 20 years or more after the onset of the disease Occasionally the tissues of the host seem to become sensitized to the spirochetes and large destructive lesions called *gummas* result These lesions which contain very few spirochetes can occur in almost every organ of the body but are most frequent in the skin or bones

Many patients with latent syphilis do not develop late manifestations and show no evidence of syphilis at autopsy A study of patients with untreated early syphilis followed for a number of years showed that approximately one third of them achieved spontaneous cures with the development of negative serologic tests An equal number died of causes other than syphilis or developed latent syphilis with no clinical evidence of the disease other than a positive serologic test The remaining third developed serious lesions of the cardiovascular or central nervous system or benign gummatous lesions of the skin or bones

Histopathology The early lesions of syphilis are characterized by infiltration of the blood vessel walls and perivascular spaces with plasma cells large mononuclear cells and lymphocytes Spirochetes can be demonstrated by silver impregnation stains In the late lesions of syphilis there may be necrosis with granuloma or gumma formation The necrosis is thought to be the result of an exaggerated or hypersensitive response to a small number of organisms Spirochetes are rarely found These lesions heal slowly and often produce large scars

Immunity and Resistance The development of immunity in a syphilitic patient can be considered from two standpoints the resistance the patient

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Section 11 Spirochetal Infections

153 SYPHILIS

Albert Heyman

Definition Syphilis is a chronic systemic infectious disease caused by the *Treponema pallidum* and usually transmitted by sexual contact It is capable of producing tissue destruction and chronic inflammation in almost any organ in the body and *can express itself in a great diversity of clinical* manifestations

History Considerable knowledge of the pathology and clinical aspects of syphilis was accumulated in the sixteenth to nineteenth centuries but it was not until early in the present century that most of the fundamental information about the disease was uncovered The etiologic agent the *T pallidum* was discovered by Schaudinn and Hoffmann in 1905 Soon afterward Wassermann and his associates introduced serologic methods of diagnosis In 1949 Nelson and Mayer introduced the *T pallidum* immobilization test following which other tests for demonstrating humoral antibodies were subsequently developed

In 1910 Ehrlich announced the discovery of arsphenamine and in 1917 Wagner von Jauregg demonstrated the value of malarial fever therapy for paresis These were the two most important advances in the treatment of syphilis until 1943 when penicillin was found by Mahoney and his associates to be effective in the early stages of the disease This drug has largely replaced the other forms of chemotherapy in syphilis

Etiology The *T pallidum* is a slender spirochete *with regular evenly spaced spirals* It varies in length from 5 to 20 μ When viewed under the dark field microscope *T pallidum* shows characteristic motility rotating on its long axis and moving slowly backward and forward The spirals usually keep their uniform shape and size although the body of the organism may bend at the middle It does not have the quick whipping movements of other spirochetes which are often found in ulcerative lesions The organism does not stain well with ordinary dyes but can be demonstrated by silver impregnation methods in fixed tissues For clinical purposes it can be demonstrated by dark field microscopy of material from primary or secondary syphilitic lesions

Treponema pallidum is readily killed by soap

administered during this period of time If the dark field examinations and serologic tests for syphilis are negative the serologic test should be repeated several times during the first 2 or 3 weeks and every few weeks thereafter for 3 months after the appearance of the lesion If the patient develops a positive serologic reaction in a high or rising titer (with or without evidence of secondary manifestations) then antisyphilitic therapy should be begun A *single serologic test* of low titer is not sufficient evidence for beginning antisyphilitic treatment if dark field examinations are negative Such tests should be confirmed several times for at least 2 or 3 weeks before treatment for syphilis is justified

Penicillin or other spirocheticidal drugs should not be given as a therapeutic test to patients suspected of having primary syphilis Healing of the genital lesion following such tests does not necessarily indicate the presence of syphilis since nonsyphilitic lesions sometimes heal spontaneously Biopsy of the genital lesions is often of value in the diagnosis of these patients

Secondary Stage The secondary stage of syphilis usually develops about 6 weeks after appearance of the chancre and is manifested by a generalized skin eruption and systemic symptoms Some patients exhibit secondary lesions without ever being aware of a primary others never develop secondary manifestations and enter the latent stage directly following the healing of the chancre

The appearance of the *cutaneous lesions* of secondary syphilis varies considerably and may be confused with many other skin eruptions The lesions most often found are papules maculopapules or follicular papules Occasionally annular pustular or rupial lesions occur Indeed almost any type of skin eruption may appear except a vesicular one The rash is usually widespread and frequently involves the palms soles and face in addition to the trunk and extremities The lesions are sometimes pruritic

The *mucous membranes* of the mouth and genitalia are often involved in secondary syphilis Syphilitic lesions of the mouth appear as painless superficial erosions on the buccal surfaces on the tongue or inside the lip When these lesions are covered with a thin grayish exudate they are known as *mucous patches* They contain a large number of spirochetes but may be very inconspicuous and the patient may not be aware of them Lesions of the palate and tonsillar area can cause a persistent *sore throat* So called *split papules* are occasionally seen in secondary syphilis and may be mistaken for herpes benign fissures or the lesions of riboflavin deficiency

Syphilitic mucosal lesions of the genitalia or perianal regions often become hypertrophic and are called *condylomata lata* These lesions are broad flat wartlike excrescences which are found on the labia majora perineum and anal region They are highly *infectious* and should be *differentiated from* condylomata acuminata which are nonvenereal pedunculated lesions

Although the clinical findings of secondary syphilis are often confined to the skin and mucous membranes many patients will present evidence of *constitutional symptoms* and widespread spirochetal dissemination Malaise lassitude headaches fever and myalgia are often noted There may be a *generalized lymphadenopathy* Localized areas of *alopecia* also occur causing a "moth-eaten" appearance of the scalp

Approximately 4 per cent of patients with secondary syphilis have involvement of the eye usually *iritis* or *neuroretinitis*

Skeletal lesions occasionally occur in secondary syphilis and are manifested by localized areas of swelling and tenderness *Arthralgia* and *hydrarthrosis* also occur but changes in the joints cannot be detected by x ray examination An acute *nephrosis* with marked proteinuria edema and hypercholesteremia is sometimes seen in secondary syphilis Evidence of *central nervous system involvement* such as paralysis of the cranial nerves or meningitis may also appear in this stage of the disease

It is apparent from the above description that secondary syphilis may be manifested by a great variety of apparently unrelated clinical symptoms Although isolated lesions such as iritis or periostitis may not in themselves suggest the diagnosis the recognition of other symptoms such as sore throat lymphadenopathy or skin lesions will often make the diagnosis of secondary syphilis obvious Whenever secondary syphilis is suspected blood should be taken for a serologic test This will be positive in practically 100 per cent of the cases Conversely if the serologic test is negative (and technical errors excluded) secondary syphilis can be ruled out

INFECTIOUSNESS AND EPIDEMIOLOGY

Syphilis is most infectious during the primary and secondary stages when there are moist skin or mucosal lesions The genital condylomas and the oral mucosal lesions contain large numbers of spirochetes and are more infectious than the dry skin lesions The transmission of the disease by individuals or marital partners who deny having had open lesions is probably by way of small mucosal lesions which appear during the recurrent episodes of spirochetemia Some secretions such as saliva and semen are frequently in contact with infectious mucosal lesions and may thus contain *T pallidum* The blood of patients ...

develops to his own infection and the immunity he develops to reinfection

Practically every patient with syphilis develops some resistance to his own infection The degree of immunity determines whether the patient will achieve a spontaneous cure the disease will remain latent or late complications will develop The factors responsible for the development of this type of immunity and the destruction of spirochetes are largely unknown The serum of experimentally infected animals and patients with syphilis contains antibodies which immobilize and render noninfectious virulent strains of *T pallidum* These antibodies can be demonstrated in vitro by means of the *T pallidum* immobilization (TPI) test developed by Nelson In humans this immobilizing antibody appears during the early stages of syphilis and will usually persist indefinitely unless early adequate treatment for syphilis is instituted The antibody is not present in the serum of normal persons nor in those with nonspirochetal diseases but it occurs in the serum of patients with various treponematoses such as bejel yaws and pinta The exact relationship between this antibody and the development of immunity has not yet been determined

Humoral antibodies in syphilis have also been demonstrated by newer techniques such as the *T pallidum* immune adherence (TPIA) *T pallidum* agglutination (TPA) and *T pallidum* complement fixation (TPCF) tests These procedures for detecting syphilitic antibodies are still in the experimental stage

Apparently the outcome of the syphilitic infection is influenced to some extent by the sex and race of the individual Neurosyphilis for example occurs more frequently in men than in women and in a higher proportion of white individuals than Negroes Bone and cardiovascular syphilis are more common in Negroes

Immunity to reinfection develops soon after the onset of the disease In animals immunity has been found to appear within 3 weeks after the initial infection and to increase progressively during a period of 6 months In humans reinoculation usually results in a chancre if carried out within 15 days after the appearance of the primary lesion of the initial infection Later than this a chancre seldom develops but this resistance is relative

Adequate treatment of patients with early syphilis may abort the development of immunity and reinfections can occur If treatment is delayed until after this period immunity to reinfection becomes established and may remain throughout the life time of the individual

If inadequate treatment is given during early syphilis and complete destruction of the patient s spirochetes is not obtained redissemination of the organisms may occur and produce infectious skin and mucosal lesions This is the basis for the statement that poor treatment is worse than none at all Once the patient has developed immunity to his own infection (usually within 4 years after the onset of the disease) inadequate treatment does not result in redissemination of organisms

CLINICAL MANIFESTATIONS OF EARLY ACQUIRED SYPHILIS

Primary Stage The period of incubation may vary from 10 to 90 days The typical chancre is a solitary indurated nonpainful ulceration which heals slowly with scar formation It is often accompanied by painless enlargement of the regional lymph nodes the *satellite bubo* It must be emphasized that primary syphilis is often atypical and may be manifested by small multiple or painful lesions which resemble many other conditions Because of the frequent atypical appearance of the chancre the clinical diagnosis or exclusion of primary syphilis can never be relied upon and every genital lesion should have a dark field examination

Approximately 95 per cent of primary lesions are found on or near the genitalia In the male the chancre frequently appears on the coronal sulcus or on the prepuce Any part of the genitalia may be involved however Chancres of the external genitalia must be differentiated from chancroid granuloma inguinale lymphogranuloma venereum carcinoma and many other lesions which appear in this area In the female the primary lesion often appears on the labia and in the fourchette but the perineum pubis clitoris or urethra may be involved Chancres of the cervix are frequent and are often mistaken for nonspecific erosions About 5 per cent of primary lesions occur on the lips female breasts or in the mouth

In the diagnosis of primary syphilis serologic tests cannot be relied upon entirely since they are often negative in this stage of the disease Moreover a positive serologic reaction in a patient with a genital lesion may represent either latent infection associated with nonsyphilitic lesion or else a biologic false positive reaction caused by another disease (i e lymphogranuloma venereum or chancroid) For this reason a dark field examination is of greatest importance in the diagnosis of this stage of the disease and should be done on the first visit of every patient suspected of having primary syphilis If the initial dark field examination is negative material from the regional lymph nodes should be aspirated and examined All local medication as well as antibiotics with treponemicidal activity should be withheld but oral sulfonamides may be

administered during this period of time If the dark field examinations and serologic tests for syphilis are negative the serologic test should be repeated several times during the first 2 or 3 weeks and every few weeks thereafter for 3 months after the appearance of the lesion If the patient develops a positive serologic reaction in a high or rising titer (with or without evidence of secondary manifestations) then antisyphilitic therapy should be begun A single serologic test of low titer is not sufficient evidence for beginning antisyphilitic treatment if dark field examinations are negative Such tests should be confirmed several times for at least 2 or 3 weeks before treatment for syphilis is justified

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The appearance of the *cutaneous lesions* of secondary syphilis varies considerably and may be confused with many other skin eruptions The lesions most often found are papules maculopapules or follicular papules Occasionally annular pustular or rupial lesions occur Indeed almost any type of skin eruption may appear except a vesicular one The rash is usually widespread and frequently involves the palms soles and face in addition to the trunk and extremities The lesions are sometimes pruritic

The *mucous membranes* of the mouth and genitalia are often involved in secondary syphilis Syphilitic lesions of the mouth appear as painless superficial erosions on the buccal surfaces on the tongue or inside the lip When these lesions are covered with a thin grayish exudate they are known a *mucous patches* They contain a large number of spirochetes but may be very inconspicuous and the patient may not be aware of them Lesions of the palate and tonsillar area can cause a persistent *sore throat* So-called *split papules* are occasionally seen in secondary syphilis and may be mistaken for herpes benign fissures or the lesions of riboflavin deficiency

Syphilitic mucosal lesions of the genitalia or perineal regions often become hypertrophic and are called *condylomata lata* These lesions are broad flat wartlike excrescences which are found on the labia majora perineum and anal region They are highly infectious and should be differentiated from condylomata acuminata which are nonvenereal pedunculated lesions

Although the clinical findings of secondary syphilis are often confined to the skin and mucous membranes many patients will present evidence of *constitutional symptoms* and widespread spirochetal dissemination Malaise lassitude headaches fever and myalgia are often noted There may be a *generalized lymphadenopathy* Localized areas of *alopecia* also occur causing a "moth-eaten" appearance of the scalp

Approximately 4 per cent of patients with secondary syphilis have involvement of the eye usually *iritis* or *neuroretinitis*

Skeletal lesions occasionally occur in secondary syphilis and are manifested by localized areas of swelling and tenderness *Arthralgia* and *hydrarthrosis* also occur but changes in the joints cannot be detected by x ray examination An acute *nephrosis* with marked proteinuria edema and hypercholesteremia is sometimes seen in secondary syphilis Evidence of *central nervous system involvement* such as paralysis of the cranial nerves or meningitis may also appear in this stage of the disease

It is apparent from the above description that secondary syphilis may be manifested by a great variety of apparently unrelated clinical symptoms Although isolated lesions such as iritis or periostitis may not in themselves suggest the diagnosis the recognition of other symptoms such as sore throat lymphadenopathy or skin lesions will often make the diagnosis of secondary syphilis obvious Whenever secondary syphilis is suspected blood should be taken for a serologic test This will be positive in practically 100 per cent of the cases Conversely if the serologic test is negative (and technical errors excluded) secondary syphilis can be ruled out.

INFECTIOUSNESS AND EPIDEMIOLOGY

Syphilis is most infectious during the primary and secondary stages when there are moist skin or mucosal lesions The genital condylomas and the oral mucosal lesions contain large numbers of spirochetes and are more infectious than the dry skin lesions The transmission of the disease by individuals or marital partners who deny having had open lesions is probably by way of small mucosal lesions which appear during the recurrent episodes of spirochetemia Some secretions such as saliva and semen are frequently in contact with infectious mucosal lesions and may thus contain *T pallidum* The blood of patients with early syphilis has

been shown to contain spirochetes and should not be used for transfusion The serologic test is not always an indication of the infectiousness of the blood since transfusion syphilis can be transmitted from patients in the incubation period or in the seronegative primary stage of the disease The danger of *transmitting syphilis either by transfusion* or by direct contact is greatest in the first 4 years of the disease and is negligible after this period of time In pregnancy however the disease can apparently be transmitted to the fetus for as long as 10 years or more after the onset of the disease although the vast majority of congenital infections are acquired during the first 4 years of maternal infection

It is important that the physician make an effort to determine the source of infection of his patients with syphilis particularly those with primary and secondary manifestations It is equally important that the individuals to whom the patient may have transmitted the infection be located They should be followed with physical examinations and serologic tests for several months before being dismissed

LATENT SYPHILIS

Latent syphilis is that stage of the disease in which there are no clinical signs or symptoms of the infection Patients without signs or symptoms *but with abnormal spinal fluid findings have a much* more serious prognosis and are not regarded as having latent syphilis but are classified instead as having asymptomatic neurosyphilis

Latent syphilis is by far the most frequent type of syphilis Routine serologic testing is the only way in which the majority of patients with latent syph*ilis can be recognized*

Although the syphilitic infection is not clinically evident during the latent period it may be producing serious changes in the viscera Often the spirochete exists within the body throughout the entire lifetime of the host without producing any apparent effects upon health and longevity Most of the patients with late latent syphilis develop sufficient resistance to their infection to prevent late clinical manifestations

The diagnosis of latent syphilis is one of exclusion and a careful history and physical examination should be made for clinical evidence of this disease Since the diagnosis of latent syphilis is dependent upon the serologic test false positive reactions must be ruled out *Treponema pallidum* immobilization (TPI) tests or the newer *T pallidum* complement fixation test (TPCF) should probably be carried out routinely in patients with positive serologic tests in whom there is no history or clinical evidence of syphilis and in whom the diagnosis seems unlikely

CLINICAL MANIFESTATIONS OF LATE ACQUIRED SYPHILIS

Skin and Mucous Membranes Late syphilis of the skin may appear either as small nodules or ulcerating gummas The gumma begins as a pain*less subcutaneous tumor which gradually softens* and ruptures exuding a viscous gummy material Spirochetes are seldom found in these lesions The nodular form of late syphilis consists of slightly raised reddish brown lesions on the skin which often coalesce to form arciform or serpiginous configurations

Gummas also occur in the mucous membranes of the nose and throat and may produce painful destructive lesions in the palate and nasal septum

Skeletal System Late osseous syphilis often presents a difficult diagnostic problem The chief symptoms are pain tenderness and local warmth The bones usually involved are the skull and tibia although the clavicle humerus ribs and nasopalatine structures are sometimes affected

Syphilis of the skeletal system is often confused with other types of subacute or chronic osteomyelitis primary or secondary neoplasms or Paget s disease The diagnosis can usually be made by close correlation of the serologic clinical and roentgenographic findings In some instances biopsy may be necessary

The most common joint manifestation occurring in late syphilis is the *Charcot joint* This condition is not caused directly by *T pallidum* but develops as a consequence of destruction of the proprioceptive nerves in tabes dorsalis It also occurs in other neurologic disorders such as syringomyelia The Charcot joint is usually confined to a *single weight bearing joint such as the knee ankle or* hip and occasionally the spine It begins as a painless swelling of the joint and is later manifested by hypermobility and loss of contour The joint surface disintegrates so that fragments of bone and cartilage can be felt within the joint capsule Charcot joints often appear in arrested or "burnt out cases of tabes dorsalis—i e patients with normal blood and spinal fluid findings Antisyphilitic drugs are of little value in treatment and orthopedic measures are usually necessary

Liver In patients with late syphilis *the liver may* contain multiple minute gummatous lesions or several very large ones On healing these lesions produce scarring and contraction of the surface giving the liver the appearance of having several additional lobes—hence the name *hepar lobatum* The most common *finding on physical examination is a* large coarsely nodular irregular liver Ascites jaundice and splenomegaly are occasionally present The serologic test for syphilis is almost always positive Response to treatment is often dramatic

with rapid reduction in liver size and relief of symptoms

Stomach Late syphilis of the stomach consists of a diffuse granulomatous infiltration of the stomach wall or a localized annular constriction about the pyloric area Secondary ulceration and obstruction may occur so that differentiation from carcinoma by roentgenographic examination is often impossible Syphilis of the stomach may be suspected in young individuals on the basis of the roentgenographic appearance of the lesion and a positive serologic test but exploratory laparotomy is usually indicated to confirm the diagnosis

Larynx Syphilis of the larynx produces hoarseness without pain Laryngoscopic examination may reveal gummatous infiltration of the vocal cords with secondary ulceration The lesions may simulate carcinoma or tuberculosis and biopsy is necessary for differential diagnosis *Treatment* of this condition should be cautious since intensive therapy has been known to produce edema stridor and suffocation Patients with late syphilis may also develop hoarseness without pain as a result of recurrent nerve paralysis caused by aneurysm of the aorta

Kidney and Genitourinary Tract An acute nephrotic syndrome occasionally appears in early syphilis In late syphilis a specific type of interstitial nephritis may be present on postmortem examination without having produced a characteristic clinical picture Gumma of the kidney is rare but late syphilis of the bladder testes and penis is occasionally reported Paroxysmal hemoglobinuria is sometimes caused by syphilis It is discussed in another section (see p 1187)

In the female late syphilis rarely involves the internal genital organs but gummatous lesions sometimes appear in the breast

Involvement of the endocrine glands such as the adrenals thyroid and pituitary gland is also infrequent

Cardiovascular Syphilis Since cardiovascular syphilis is discussed fully elsewhere (p 1336) it will be mentioned only briefly at this point Cardiovascular syphilis is one of the most important of the late lesions of syphilis and probably accounts for the majority of deaths resulting from this disease It is much more common in men than in women and seems to be more frequent in Negroes than in whites It usually appears in the second to third decade after infection and may be associated with neurosyphilis and other late manifestations

The fundamental lesion of cardiovascular syphilis is *aortitis* *Treponema pallidum* causes destruction of the media fragmentation of the elastic material and eventual dilatation of the vessel The base of the aorta is often involved with dilatation of the valve ring and *aortic insufficiency* If the weakening is localized a saccular *aneurysm* may develop The intima of the aorta becomes thickened and occlusion of the orifices of the coronary arteries may occur A few cases of multiple gummas of the *myocardium* have been reported but the existence of a diffuse syphilitic myocarditis is a matter of controversy

Central Nervous System Neurosyphilis together with cardiovascular syphilis accounts for about 90 per cent of deaths caused by syphilis Although all the tissues of the central nervous system are invaded by the spirochetes the clinical symptoms may be arbitrarily divided into meningeal vascular and parenchymatous Meningeal and vascular symptoms usually develop early in the course of the disease whereas parenchymatous involvement as manifested by tabes dorsalis and paresis usually does not appear until 10 to 20 years after the primary infection Meningeal lesions are inflammatory and often reversible Parenchymatous lesions however are likely to be degenerative with irreversible damage The type of lesion which predominates the structures involved and the exact location of the lesion within the central nervous system are the three important factors which influence prognosis and response to treatment

Gummas of the brain and spinal cord are occasionally observed They produce symptoms similar to tumors of the central nervous system and differentiation is difficult

Asymptomatic Neurosyphilis Asymptomatic neurosyphilis is that stage of the disease in which an abnormal spinal fluid exists without clinical signs or symptoms to indicate that the function of the central nervous system has been affected

The outcome of asymptomatic neurosyphilis and the extent of the spinal fluid abnormalities appear to be definitely related since patients exhibiting marked changes are more likely to develop signs and symptoms Some workers believe that the activity of the neurosyphilitic process is related to the spinal fluid cell count and protein level The presence of a positive spinal fluid Wassermann reaction indicates that infection of the central nervous system has occurred the cells and protein indicate the activity of the condition This concept maintains that if the spinal fluid is inactive—i e if the cell count and protein are normal—the syphilitic infection in the central nervous system has been arrested and no further therapy is needed Although this concept is not completely accepted it seems to hold true in the majority of patients

The serologic reaction of the blood does not always parallel the spinal fluid findings Patients with previous treatment may have a negative blood test and a strongly positive spinal fluid This combination seldom occurs in untreated cases

If the spinal fluid is completely negative 5 years

after the onset of the disease it rarely if ever becomes positive again

Meningitis In a small number of patients involvement of the central *nervous system may* be manifested by an acute meningitis This condition usually appears within the first 2 years after the onset of syphilis It nearly always occurs in patients who have previously had inadequate therapy and may be associated with an infectious or mucocutaneous relapse

The symptoms usually consist of cranial nerve lesions delirium convulsions or signs of increased intracranial pressure *Papilledema* is frequently found in patients with syphilitic meningitis and these cases are often diagnosed erroneously as having *brain tumors*

The serologic test for syphilis and the spinal fluid Wassermann are usually strongly positive The spinal fluid may show a marked lymphocytosis counts as high as 2 000 cells per cu mm having been observed This condition is often confused with other forms of lymphocytic meningitis such as tuberculous or virus meningitis The immediate prognosis is good but the ultimate prognosis is much more serious If the patient does not receive *adequate treatment late manifestations* of neurosyphilis or paresis are likely to develop

Meningovascular Syphilis Meningovascular syphilis is usually manifested by signs of thrombosis of one or more of the branches of the cerebral or spinal arteries Since there is almost always some evidence of leptomeningitis the term meningovascular syphilis is used to describe these cases

The symptoms of this condition depend upon the location and size of the vessels involved Monoplegia or hemiplegia hemianesthesia aphasia or hemianopsia may occur Cranial nerve palsies are frequent and convulsions are often observed Syphilitic endarteritis may also involve the cerebellar vessels Patients with meningovascular syphilis sometimes develop psychotic behavior and differentiation from paresis is often difficult

In older patients it is often impossible to differentiate clinically between syphilitic vascular disease and a cerebral vascular accident of other etiology In such cases the blood and spinal fluid findings provide the only means of differentiation The blood serologic test is positive in the majority of patients with vascular neurosyphilis and the spinal fluid usually shows a moderate increase of cells and protein with a positive Wassermann reaction A diagnosis of meningovascular syphilis should not be made if the spinal fluid is normal

The vessels and meninges of the spinal cord undergo *changes* identical with those in the brain With thrombosis of the *anterior spinal artery* the patient may *suddenly* develop signs of an acute *transverse myelitis* with paraplegia loss of sensation and fecal or urinary incontinence Usually however meningovascular lesions of the spinal cord are insidious and produce chronic progressive paralyses and *sensory disturbances* A number of neurologic syndromes result from more or less localized spinal cord lesions syphilitic involvement of the pyramidal tract produces the so called *Erb s spastic spinal paraplegia* anterior horn cell degeneration causes a picture similar to *progressive muscular atrophy* while a single localized *gumma* may simulate cord tumor

The term *meningovascular syphilis* is also employed for a large group of patients with diverse signs and symptoms such as *epilepsy eighth nerve deafness* other cranial nerve lesions or chronic headaches Pupillary abnormalities are frequently present and may consist of a variety of changes such as miosis dilatation anisocoria fixed pupils or typical Argyll Robertson phenomena

Tabes Dorsalis (Locomotor Ataxia) Tabes dorsalis is a form of neurosyphilis in which there is selective degeneration in the posterior roots of the spinal nerves and the posterior columns of the spinal cord Microscopically the dorsal roots may appear completely demyelinated and there is marked loss of nerve fibers The posterior *columns* of the spinal cord also show a loss of myelin and degeneration of the axons Spirochetes are rarely found in these lesions In the majority of cases tabes appears 20 to 30 years after the initial infection It is found more commonly in men than in women

Patients with tabes frequently develop severe agonizing *shooting* or *lightning* pains in the legs Girdle pains also occur in tabetics along with paresthesias numbness and tingling of the trunk hands or feet Another type of severe pain occurs in attacks of *gastric crises* About 10 per cent of tabetic patients develop severe episodes of abdominal pain associated with nausea and vomiting These attacks may last for days resulting in dehydration and exhaustion Patients with gastric crises are sometimes diagnosed as having acute surgical conditions and unnecessary operations have been performed on these individuals

Ataxia is a major symptom in tabes and may be so severe that the patient is unable to walk or stand Some patients develop a typical tabetic gait which consists of slapping of the feet and walking on a broad base The ataxia is worse in the dark and the patient may sway or fall when standing with his eyes closed (Romberg s sign) The damage to the nerve fibers in the posterior columns not only results in ataxia but also produces loss of position sense and the patient does not know without visual assistance the exact position of his toes or feet Vibratory sensation in the legs is diminished or absent There may be diminution of deep pain

sensation to pressure on the testes or Achilles tendon and areas of hypesthesia may be present on the trunk or in the hands and feet The patella and Achilles tendon reflexes are sluggish or absent Patients with tabes often show evidence of hypotonia and hyperextensibility of the joints Degenerative lesions such as chronic nonhealing lesions of the skin and *Charcot joints* are also found

Involvement of the autonomic nervous system may occur in patients with tabes and *postural hypotension* is occasionally present Severe *paroxysmal hypertension* associated with gastric crises has also been observed and may simulate paroxysmal hypertension caused by pheochromocytoma

Urinary difficulties occur in approximately 50 to 60 per cent of patients with tabes These often appear early in the disease and consist of hesitancy or difficulty in starting micturition Later the patient develops complete loss of bladder sensation Patients with tabetic bladder often give no history of urinary symptoms and catheterization for residual urine should be done in all who have evidence of tabes *Impotence* and loss of sexual desire are frequently noted

Paralysis of the oculomotor nerves is common in tabes resulting in diplopia ptosis of the lids or ophthalmoplegia Pupillary abnormalities are also extremely common and may be manifested by the classic *Argyll Robertson phenomena* that is miosis reaction to accommodation but no reaction to light poor response to atropine and absence of cilio spinal reflex This condition must be differentiated from *Adie s pupil* which is usually unilateral is larger than the normal pupil and reacts slowly to both light and accommodation Patients with Adie s pupils may also have absent or diminished tendon reflexes

Atrophy of the optic nerve occurs in about 10 to 15 per cent of patients with tabes About 70 per cent of patients with untreated optic atrophy become blind in *3 years and 90 per cent in 5 years* On ophthalmoscopic examination the optic disk appears white and sharply defined The physiologic cup is prominent and the lamina cribrosa is abnormally conspicuous Visual field defects and diminution of vision may be present with only slight changes in the color of the disks To detect such cases of optic atrophy early careful perimetry and visual acuity examinations should be made in all cases of neurosyphilis Although improvement in vision is not to be expected in patients with optic atrophy arrest of the atrophic process can usually be obtained by penicillin therapy in patients with early involvement

In early cases of tabes the serologic test for syphilis is often strongly positive and the spinal fluid may show definite abnormalities such as increased cells and protein and a positive Wassermann In patients with long standing tabes however the blood and spinal fluid findings may be misleading Approximately one fourth of such patients have negative blood serologic tests while as many as 20 per cent have normal spinal fluids Tabes dorsalis must be differentiated from numerous other diseases of the spinal column such as cord tumor combined system disease and syringomyelia as well as various types of peripheral neuritis (particularly diabetic neuropathy) The response of tabes to treatment is often poor and symptoms may progress despite all forms of therapy

Paretic Neurosyphilis (Dementia Paralytica Paresis General Paralysis of the Insane) General paresis is a psychosis caused by extensive spirochetal invasion of the brain On histologic examination the most prominent feature is degeneration of the nerve cells Perivascular infiltration and endothelial proliferation of the small vessels is seen *Treponema pallidum* can be demonstrated in the cerebral cortex and other portions of the brain

Paretic neurosyphilis is more common in men than in women and usually develops between the ages of thirty five and fifty years The onset is most often insidious prodromal symptoms consist of headache insomnia difficulty in concentration and easy fatigability As the disease progresses a gradual change in personality takes place with increased irritability memory loss poor judgment lack of personal care and deviations in character These alterations may occur over a period of several months Many of them are noted by the patient s family only in retrospect and elicited only by close questioning The onset of paresis is sometimes sudden and may be ushered in by convulsions syncope or a cerebral vascular accident

The simple demented type of psychosis is the most common These patients show confusion apathy impaired memory and defects in judgment Memory is particularly poor for recent events They are often unable to concentrate on simple calculations and show little insight or concern about their illness The grandiose form of paresis is manifested by euphoria overactivity ideas of grandeur and megalomania Auditory and visual hallucinations are not common in these patients but delusions of wealth and prowess are frequent The type of psychosis that prevails in a given case depends to a great extent upon the preparetic personality of the individual As the disease progresses however the symptoms of euphoria paranoia or mania recede and simple deterioration and dementia become the outstanding features

Eventually the patients become completely bedridden and are unable to move and feed themselves

On neurologic examination these patients may present various motor disturbances such as *tremors* of the facial muscles tongue and outstretched

after the onset of the disease it rarely if ever becomes positive again

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ous modifications of flocculation tests for syphilis have been named after their originators (Kahn Eagle Mazzini Kline and Hinton) The complement fixation technique or Wassermann test employs the same type of antigen The Kolmer and Eagle modifications of the Wassermann technique are most commonly used in this country The VDRL (Venereal Disease Research Laboratory) test is a rapid slide flocculation technique employing cardiolipin antigen It has a high degree of sensitivity and specificity

Quantitative serologic tests for syphilis measure the quantity of reagin and are of value in the diagnosis and management of various stages of the disease A sharply rising titer is usually found in recently acquired syphilis while a stationary titer indicates an infection of some duration Quantitative serologic tests are also useful in the detection of false positive reactions A rapidly falling titer in the absence of therapy is evidence against the diagnosis of syphilis The height of the quantitative titer has no bearing on the prognosis or outcome of the disease The quantitative tests are also important in determining the results of therapy a continuing fall in titer indicates a satisfactory response

The presence of a negative reaction does not always exclude syphilis nor is a positive reaction always proof of the existence of the disease Serologic tests are negative in the incubation period of syphilis during the early weeks of the primary stage and in many of the late manifestations such as cardiovascular and neurosyphilis (tabes dorsalis in particular)

Biologic False Positive Serologic Tests for Syphilis Positive reactions appear in a great variety of illnesses and are due presumably to the appearance in the patient s serum of substances which act like reagin and give positive flocculation and complement fixation reactions for syphilis These reactions are usually transient but in some instances may be positive for months or years

Biologic false positive reactions are frequently observed in patients with vaccinia infectious mononucleosis malaria leprosy and upper respiratory diseases as well as in spirochetal infections such as yaws pinta and relapsing fever Other infections which are occasionally associated with false positive reactions are lymphogranuloma venereum chancroid measles chicken pox atypical pneumonia infectious hepatitis rat bite fever and disseminated lupus erythematosus In fact any febrile disease or immunization is a potential cause of false positive tests There is evidence that individuals with biologic false positive reactions of long duration may have serious illnesses such as collagen disorders sarcoid or lymphomas

The *Treponema pallidum* immobilizing (TPI) test of Nelson and the newer *T pallidum* complement fixation (TPCF) test are often of considerable aid in the diagnosis of false positive reactions These tests are almost always positive in late syphilis A negative TPI or TPCF test is therefore of value in excluding the diagnosis of syphilis A positive test on the other hand indicates the existence of a syphilitic infection even if the standard serologic tests are negative In most cases the false positive reaction will become negative within 6 months If the patient continues to show a positive serologic test and if the adjunct procedures do not indicate a false positive reaction antisyphilitic therapy should be instituted If the patient becomes pregnant or is to be married immediate treatment is indicated

Seroresistance In many patients with syphilis the serologic test remains positive despite prolonged intensive therapy These patients are called seroresistant or Wassermann fast One of the aims of therapy in early syphilis (particularly during the first 2 years of the disease) is to procure and maintain a negative serologic reaction In late syphilis however seroresistance is of little clinical importance and has no relationship to the outcome of the disease

In most patients with early syphilis the serologic test becomes negative within 6 months after beginning therapy Occasionally the titer of the serologic reaction falls very slowly and the tests remain positive in low titer (i e less than 4 dilution) for as long as 1 to 2 years In some patients with early syphilis there is very little serologic response to treatment and the titer remains high for 6 to 9 months or more This type of seroresistance is usually followed by clinical relapse and these patients should be re treated

Neurosyphilis is frequently associated with seroresistance in both early and late cases and the spinal fluid should be examined in every patient with a persistently positive serologic reaction

The seroresistant patient is often discouraged over the failure to reverse the serologic test and becomes deeply concerned for fear that the infection is not arrested In addition he may be embarrassed in applying for a marriage license or employment when blood tests are a part of the premarital or preemployment examination The physician should make every effort to reassure such patients that the outcome of the disease is not related to the persistence of a positive serologic test Seroresistance should not be an obstacle to marriage

Spinal Fluid Tests The spinal fluid must be examined in every patient with syphilis This is the only method of detecting involvement of the central nervous system in the asymptomatic stage of determining the efficacy of treatment and of confirming the diagnosis of symptomatic neurosyphilis

hands The patient s handwriting is altered because of the tremors and incoordination The speech becomes slurred and test phrases are mispronounced Pupillary abnormalities are common and deep reflexes are usually exaggerated Some patients with paresis also have signs and symptoms of tabes—i e, *taboparesis*

The demented form of paresis must be differentiated from senile dementia and Alzheimer s disease The manic and paranoic types must be distinguished from manic depressive psychoses and schizophrenia In the early stages of paresis differentiation from neurasthenia is sometimes difficult and spinal fluid examination may be the only means of diagnosis

The spinal fluid in general paresis shows marked *changes with increased cells and protein positive* Wassermann test and first zone colloidal reaction The diagnosis of paresis should never be made in the presence of a normal spinal fluid a positive spinal fluid is present in 100 per cent of untreated cases

The course of untreated paresis is progressive and death usually occurs within a few years after the onset of symptoms The prognosis improves considerably with therapy but the chances for complete recovery are at best about 50 to 60 per cent

SYPHILIS IN PREGNANCY

Syphilis in pregnancy is a special problem because the fetus becomes infected after the fifth month of pregnancy by passage of *T pallidum* through the placenta This usually occurs in women with early untreated syphilis but is sometimes observed in late syphilis Pregnancy complicated by syphilis may terminate in a spontaneous abortion a stillborn infant or a premature or full term infected child The maternal infection however *becomes attenuated as the duration of the disease* increases and the chances of the fetus being infected are less with each succeeding pregnancy

Pregnancy is believed to have a beneficial influence upon the course of the syphilitic infection and late manifestations of the disease seem to occur less frequently in multiparous women than in others A serologic test for syphilis should be taken routinely at the first prenatal visit of every pregnant woman The early recognition of syphilis in pregnancy followed by adequate treatment will prevent congenital syphilis in almost every instance

CONGENITAL SYPHILIS

Infantile congenital syphilis is often an overwhelming infection such infants are severely ill malnourished and dehydrated The most common manifestations of the disease in infants are skin lesions fissures condylomas persistent rhinitis tenderness over the long bones and pseudoparalysis

The diagnosis of syphilis in the infant is best established by dark field demonstration of *T pallidum* from the cutaneous or mucosal lesions A positive serologic test in the first two months of life does not always indicate syphilis in the infant since reacting substances may have been transferred from the maternal circulation A very high titer of the serologic reaction or a steady rise in titer however is indicative of congenital syphilis Roentgenographic examination of the long bones may show characteristic areas of bone destruction and *osteochondritis*

Late congenital syphilis frequently manifests itself *in the* second decade with signs of central nervous system involvement such as eighth nerve deafness optic atrophy and *juvenile paresis* The prognosis of congenital neurosyphilis is serious these patients commonly show little response to treatment Cardiovascular syphilis is rare in the congenital infection

Patients with late congenital syphilis often exhibit typical stigmas such as hypoplasia wide spacing and notching of the central incisors (*Hutchinson teeth*) frontal bossing a highly arched palate and *saber shins* The first permanent molar is also frequently affected in congenital syphilis and shows a characteristic appearance with several small atrophic cusps on the occlusal surface This is known as a mulberry molar *Interstitial keratitis* a frequent complication usually appears in the second decade It is characterized by pain lacrimation circumcorneal injection and corneal opacity The response to therapy is poor and serious impairment of vision often results Occasionally hydrarthrosis of the knee joint (*Clutton s synovitis*) is associated with interstitial keratitis

LABORATORY DIAGNOSIS

Dark field demonstration of *T pallidum* is most useful in the early stages of syphilis It should be employed routinely on every genital lesion and on all cutaneous and mucosal lesions suspected of being syphilitic In the hands of a competent microscopist dark field examination is reliable and establishes without doubt the diagnosis and stage of the infection

Serologic Tests Serologic tests for syphilis (STS) *are the most commonly used diagnostic procedures* In latent syphilis they are the only means by which the diagnosis can be made The serologic tests are based upon the presence of an antibodylike substance (sometimes called *reagin*) which appears in the patient s serum soon after the onset of the disease Syphilitic serum reacts with an antigen made from an alcoholic extract of beef heart Vari

other course of therapy with penicillin is indicated

Serologic tests should be taken at 3 month intervals during the second year after treatment and at 6-month intervals during the third fourth and fifth years If at the end of 5 years the patient has no clinical evidence of syphilis and has a normal blood and spinal fluid he may be considered completely cured

A spinal fluid examination should be performed 6 months after the completion of treatment for early syphilis If it is normal at this time and if the patient continues to show no evidence of clinical or serologic relapse it need not be repeated until approximately two years following treatment Patients having positive spinal fluid tests for syphilis 6 months or more after treatment for early syphilis should be re treated

Relapse and Reinfection Evidence of relapse in early syphilis may occur as early as 4 weeks or as late as 2 years after treatment

The prognosis of relapsing syphilis is more serious than the initial infection and such patients should be re treated with twice the original dose of penicillin given over a longer period of time Many patients with recurrent syphilis actually have a new infection rather than a relapse of their original infection Although various criteria have been set up to distinguish relapse from reinfection differentiation is often impossible

Syphilis in Pregnancy Congenital syphilis can be prevented by proper treatment of syphilis in pregnancy Although women with syphilis of many years duration are not likely to bear syphilitic children further treatment of such patients during pregnancy is recommended Although treatment with penicillin is of considerable value when given during the last months of pregnancy it is best given before the fetus becomes grossly infected i e before the last trimester

All patients treated for syphilis in pregnancy should be observed very closely and quantitative serologic tests for syphilis taken at least every month Re treatment during pregnancy is indicated if there is a rise in serologic titer following therapy if a definite decrease in titer fails to occur in patients with early syphilis or if the patient develops recurrent syphilitic lesions A positive serologic test at the time of delivery does not necessarily indicate that treatment has been inadequate The child born of a mother treated for syphilis should have a serologic test every 2 to 4 weeks until it is at least six months of age Once the woman has received adequate amounts of penicillin for syphilis it is not necessary to re treat her during succeeding pregnancies if the titer of the serologic test is negative or remains low (less than 1 4)

Congenital Syphilis Infants with congenital syphilis should receive careful supportive care and adequate nutrition in addition to antisyphilitic treatment Penicillin is very effective a total dosage of 200 000 units per kg body weight given in equally divided amounts every 3 hr for 7 to 10 days is adequate Although the use of procaine penicillin in a large series of these cases has not been reported this type of penicillin should also give satisfactory results Doses of 150 000 units of procaine penicillin in aqueous solution given every day for eight injections are recommended Follow up blood tests and the indications for re treatment in early congenital syphilis are the same as in early acquired syphilis

Treatment of interstitial keratitis is not altogether satisfactory Penicillin therapy is recommended but it does not always result in reduction of the inflammation or clearing of the corneal opacities Occasionally interstitial keratitis appears for the first time during or immediately after what appear to be adequate dosages of penicillin It seems probable that this ocular manifestation represents a type of hypersensitivity phenomenon Cortisone in aqueous suspension (5 mg per ml) or in ointment form should be applied to the involved eye every few hours day and night for several weeks The inflammatory reaction often recurs however after the drug is discontinued and repeated courses may be necessary until spontaneous regression of the condition appears Hydrarthrosis (Clutton s synovitis) responds slowly to penicillin therapy

Late Syphilis *Latent Stage* The chief purpose in treating late latent syphilis is to prevent the development of gummatous lesions and cardiovascular syphilis Patients with late latent syphilis have negative spinal fluids and rarely if ever develop neurosyphilis

Penicillin has not been evaluated in late latent syphilis Since the prognosis of this stage of the disease is so good and since the drug is known to be effective in both early and late symptomatic syphilis it is presumed to be of value in patients with latent infection The treatment schedules suggested for early syphilis employing 4 to 6 million units of penicillin are recommended Failure of the serologic test to revert to negative after adequate treatment—i e *seroresistance*—is not necessarily a forerunner of late complications Once the patient with late syphilis has had adequate treatment additional penicillin therapy will not contribute significantly toward reversal of the blood test

Skin Bones and Viscera Gummatous lesions of the skin mucous membranes bones and viscera usually respond promptly to penicillin therapy The recommended total dosage of penicillin is greater than that employed in early syphilis and should be approximately 10 million units This can be administered as 900 000 units of procaine penicillin given every 48 hr for 12 injections The posttreatment

The spinal fluid cell count should be done within an hour after the fluid is withdrawn A count of more than 8 lymphocytes per cubic millimeter is usually considered abnormal Even a small amount of blood in the spinal fluid will affect the accuracy of the various examinations A quantitative de*termination of the spinal fluid protein should be* done in every case

Complement fixation tests for syphilis are generally regarded as being more sensitive than flocculation tests for examination of spinal fluid The spinal fluid of patients with neurosyphilis has been found to contain immobilizing antibodies for *T pallidum*

The spinal fluid may also show biologic false positive complement fixation or flocculation reactions This may be caused by a bloody tap or any condition which produces an increased protein in the spinal fluid Brain tumor bacterial or virus meningitis encephalitis or subarachnoid hemorrhage can produce a false positive test for syphilis in either syphilitic or nonsyphilitic patients

The value of colloidal precipitation tests (gold and *mastic reactions) has been overemphasized in* the diagnosis of neurosyphilis The zone of precipitation or the shape of the colloidal curve has *little* diagnostic significance

Biopsy Biopsy is a valuable diagnostic procedure especially for cutaneous lesions In late syphilis involving the lymph nodes testes or larynx it is indispensable

TREATMENT

In patients with early syphilis adequate treatment can produce an absolute or biologic cure with complete healing of lesions and reversal of serologic tests and spinal fluid findings These patients become entirely well are not infectious and do not develop any of the late manifestations of the disease

Treatment of late syphilis may not achieve these goals Despite long and vigorous therapy the serologic tests in late syphilis often remain positive Late syphilitic lesions are often associated with permanent damage and treatment may produce little or no return of function

Early Syphilis In 1943 penicillin was found to be effective in the treatment of syphilis The use of arsenicals bismuth or mercurials is rarely if ever indicated Other antibiotics such as Chloromycetin chlortetracycline and oxytetracycline have treponemicidal activity and produce healing of both early and late syphilitic lesions The ultimate place of these drugs in the treatment of syphilis has not yet been established They have the possible advantage of oral administration but are probably not as effective as penicillin and are somewhat more toxic Erythromycin and tetracycline have also been shown to have some treponemicidal action

Procaine penicillin and benzathine penicillin G have generally replaced crystalline penicillin in aqueous solution except perhaps in the very serious or far advanced stages of syphilitic infection The minimal effective total dosage of penicillin has been found to be approximately 2 4 million units Increasing the total amount of penicillin from 2 4 to 9 6 million units does not decrease the failure rate in early syphilis

The total dosage of depot penicillin usually prescribed is approximately 4 to 6 million units given over a period of 8 to 12 days This schedule will produce satisfactory results in about 90 per cent of patients The remaining 10 per cent will show clinical or laboratory changes of either a relapse or reinfection Benzathine penicillin G has also been found to be effective in early syphilis when given as a single injection of 2 4 million units or in 2 or 3 weekly doses It has the advantage from the public health standpoint of completing treatment *in a minimum period of time but is not recom*mended as a routine method of treatment Oral penicillin products are not recommended for the *treatment of syphilis The other antibiotics with* treponemicidal activity should be used only in patients in whom penicillin is contraindicated

Jarisch Herxheimer Reaction Within a few hours after the first injection of either an arsenical or penicillin about 50 per cent of patients with early syphilis experience fever malaise headache myalgia and a flare up of cutaneous lesions This is presumed to be caused by release of breakdown products of spirochetes following the injection of treponemicidal agents In early syphilis *these symp-*toms disappear within several hours and leave no permanent tissue damage In late syphilis such reactions can be disastrous if the lesions are located in such areas as the ostiums of the coronary arteries the wall of an aneurysm or the central nervous system

Posttreatment Observation After completing treatment patients should return every month during the first year for quantitative serologic tests and examination for relapsing lesions If the patient develops a recurrence of syphilitic lesions or evidence of neurosyphilis or if there is a birth of a syphilitic child re treatment is necessary If the serologic test in patients with early syphilis shows no appreciable decrease within 6 months or if the titer is elevated (arbitrarily a dilution of 1 4 or higher) 1 year after completion of therapy further treatment is indicated A positive reaction in any dilution 18 months or more after completion of treatment of primary or secondary syphilis should be considered as evidence of treatment failure, and an

Careful neuropsychiatric and spinal fluid observations should be made following treatment of all patients with neurosyphilis These should be done every 4 months during the first year twice during the second year and once a year thereafter or until the spinal fluid is completely negative and permanent regression of symptoms seems apparent In late neurosyphilis the spinal fluid Wassermann often remains positive for many years despite repeated courses of chemotherapy or fever this does not in itself indicate progression or relapse of the neurosyphilitic process

Herxheimer Reactions in Late Syphilis Exacerbations of late syphilitic lesions are not infrequently observed following the initial administration of arsenicals or penicillin Approximately one half the patients treated for paresis become temporarily worse and show increased agitation and mental confusion during the first 24 hr of penicillin treatment Other manifestations of Herxheimer reaction such as myelitis convulsions and exacerbation of lightning pains have been reported

There have been very few cases in which penicillin therapy has appeared to produce an acute exacerbation of clinical manifestations of cardiovascular syphilis Neither the use of small initial doses of penicillin nor preparatory treatment with bismuth seems indicated in an attempt to prevent Herxheimer effects

Effect of Penicillin and Other Antibiotics When Used for Other Diseases The widespread use of penicillin and antibiotics with treponemicidal properties in the treatment of various other infections has created confusion in the diagnosis and management of syphilis This is particularly true when gonorrhea is treated Patients with gonorrhea may have acquired syphilis simultaneously Although there is reason to believe that the use of penicillin and perhaps the other antibiotics frequently abort the syphilitic infection completely they may at times only delay the appearance of the lesions or prevent their development For these reasons it is recommended that all persons with gonorrhea treated with penicillin or the other spirocheticidal antibiotics should have serologic tests for syphilis at monthly intervals for at least 4 months The appearance of fever several hours after the administration of penicillin for gonorrhea is suggestive of a Herxheimer reaction and the presence of syphilis

The management of patients with positive serologic tests who have had previous penicillin therapy for other nonrelated infections is sometimes difficult If syphilitic infection is thought to be present the decision as to further therapy should be based upon the amount of penicillin already administered the type and duration of syphilitic infection the result of the spinal fluid examination and the titer of the serologic test

PROPHYLAXIS

Syphilis and the other venereal diseases can be prevented in most instances by the proper prophylactic measures during and following sexual intercourse Protection from contact with infectious genital lesions can be obtained to some degree by the use of a condom The danger of infection can also be reduced if the genitalia are washed thoroughly with soap and water immediately after exposure Although ointments containing various treponemicidal substances have been employed for many years as local prophylactic agents the use of such compounds is no longer recommended In small series of cases penicillin has been shown to prevent infection in individuals who are known to have been sexually exposed to patients with primary or secondary syphilis The use of penicillin in these cases is justified not only as an attempt to abort the infection in the exposed individual but also to prevent reinfection of the original patient who often maintains sexual relations with the contact despite instructions to the contrary

Procaine penicillin or benzathine penicillin G in doses of 1 2 million units should be given soon after exposure to persons who have had sexual contact with known or suspected cases of infectious syphilis The administration of penicillin as a routine prophylactic measure following every extramarital sexual exposure is neither practical nor advisable Persons receiving prophylactic treatment should be kept under observation if possible and should have repeated serologic tests for at least 6 months

The prophylactic treatment of nurses physicians or laboratory workers accidentally exposed to or inoculated with infectious material will depend largely upon the risk of infection in the individual case Another indication for prophylactic treatment is in pregnant women who are sexually exposed to infectious patients A full course of penicillin treatment in these cases is indicated in an effort to prevent fetal infection

PSYCHOTHERAPY

There is still considerable stigma and psychologic trauma attached to the diagnosis of syphilis and proper treatment requires more than the mere administration of chemotherapeutic agents The physician must be aware of the sociologic and psychologic aspects of this disease Patients often have a sense of shame and guilt and some of them postpone or discontinue medical care Others develop serious anxiety states and return to the physician repeatedly for reassurance that the disease has been arrested Some individuals develop syphilophobia as a result of having heard or read of the serious effects of the disease The physician should

observations and indications for re treatment of these patients are the same as those recommended above A high percentage of patients with late syphilitic lesions have abnormal spinal fluid findings and a lumbar puncture is indicated in every patient before treatment is instituted

Cardiovascular Syphilis The value of antisyphilitic therapy in late cardiovascular syphilis is difficult to determine Many syphilologists believe that treatment does not delay the ultimate development of myocardial failure or aneurysmal rupture Treatment appears to be of some value however in early aortic insufficiency uncomplicated aortitis or small asymptomatic aneurysms The risk of a serious Herxheimer reaction following initiation of penicillin treatment of these cases has been found to be minimal Preparatory bismuth therapy is probably of little value in preventing this type of reaction and most workers begin treatment with penicillin The total dosage is 10 to 15 million units of penicillin given in schedules similar to those recommended for gummatous lesions As in other types of late syphilis the serologic test often remains positive after therapy Proper management of congestive failure and restriction of physical activity of these patients is of paramount importance

Neurosyphilis The results of treatment of neurosyphilis depend largely upon the type and duration of the neuropathologic process If the predominant lesion of the central nervous system is degenerative as in tabes and optic atrophy little response to any form of treatment can be expected If the tissue reaction is chiefly inflammatory as in syphilitic meningitis rapid and almost complete return of function will occur

Fever therapy is rarely used at present even though there is evidence to indicate that its use in combination with penicillin may be more effective than penicillin alone in the treatment of selected patients with paresis optic atrophy and taboparesis

Penicillin treatment of neurosyphilis is often followed by dramatic clinical response with prompt and favorable changes in the spinal fluid Shortly after penicillin therapy there is a rapid reduction in the spinal fluid cell count and protein The spinal fluid Wassermann reaction however may not become negative for 5 years or more Penicillin produced normal spinal fluid cell counts in 85 to 90 per cent of patients treated for various types of neurosyphilis The remaining 10 to 15 per cent showed abnormal spinal fluid cell counts 6 to 12 months following treatment and were considered *treatment failures*

It is generally agreed that the response of the spinal fluid tests following penicillin is as good as that obtained with fever therapy in patients with optic atrophy paresis taboparesis and eighth nerve deafness Penicillin alone is recommended as the initial form of treatment in these cases and combined fever therapy and penicillin should be given in patients in whom re treatment is required

Penicillin alone is also the treatment of choice in patients with asymptomatic neurosyphilis syphilitic meningitis and meningovascular syphilis and in those with irreversible manifestations such as fixed pupils and Charcot joints The optimum dosage schedule has not been definitely established but doses of 10 to 15 million units are usually recommended either as the aqueous solution 100 000 units every 3 hr or as procaine penicillin in aqueous suspension 900 000 units daily

Treatment of the tabetic bladder may be very discouraging Drugs such as Mecholyl chloride and ergotamine have been employed to increase bladder tone and contraction but the results are variable In early cases the patient can be trained to micturate at regular intervals and empty the bladder by pressure on the lower abdomen In late cases surgical procedures (transurethral resection of the vesical neck suprapubic cystotomy) may be necessary Urinary tract infection should be prevented and instrumentation avoided as much as possible Charcot joints are rarely improved by antisyphilitic therapy and special orthopedic treatment is necessary The management of patients with gastric crises is sometimes very difficult In the acute attack the patient should be heavily sedated Morphine should be avoided Large doses of atropine are said to be of value in relieving the symptoms of gastric crises

In most cases of advanced optic atrophy the use of penicillin or fever alone or in combination does not prevent the development of blindness Patients with optic atrophy should be admitted to the hospital and given penicillin in aqueous solution 200 000 units every 4 hr for 13 to 17 days for a total dosage of 15 to 20 million units Re treatment with combined fever and penicillin is advised if there is definite evidence of progression

The relative value of penicillin and fever therapy in paresis has not yet been definitely determined Penicillin alone often results in marked improvement of tremors and speech and writing defects It has been reported to produce entirely satisfactory results in about 20 per cent and significant improvement in an additional 35 per cent of a large series of patients with paresis treated in a general hospital Large amounts of penicillin—15 to 20 million units in aqueous solution—should be given in schedules similar to that recommended for optic atrophy If there is no definite improvement in the paretic manifestations or if relapse occurs following an initial response treatment with combined penicillin and fever therapy is indicated In general such cases respond poorly to the second course of treatment

yaw The lesions of yaws often appear on the soles of the feet and produce painful ulcerations socalled crab yaws"

After several years late destructive lesions may appear in the skin and bones Periostitis and osteitis are found in the bones of the hands arms and legs producing characteristic dactylitis and "saber shins" Destructive lesions appear about the nose and result in severe ulcerative areas (*gangosa*) Proliferative exostoses develop in the nasal portion of the maxillary bones this is known as *goundou* Juxtaarticular nodules are also seen in the late stage of the disease Involvement of the aorta and the central nervous system has been reported but these complications are rare

Diagnosis The diagnosis of yaws can often be made on the appearance of the generalized skin eruption alone but *T pertenue* is easily demonstrated in the lesions The Wassermann and flocculation tests for syphilis are usually positive The lesions of yaws may be confused with those of leishmaniasis leprosy and tuberculosis It is often impossible to differentiate between late lesions of yaws and late gummatous syphilis

Treatment Penicillin has become the drug of choice in the treatment of yaws A single or a few injections of 1 2 million units of procaine penicillin have resulted in cure or marked improvement in more than 90 per cent of patients Benzathine penicillin G has been found to be equally effective Preliminary studies with chlortetracycline chloramphenicol and oxytetracycline indicate that these antibiotics are also of value in the management of this condition

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155 PINTA

Albert Heyman

Definition Pinta is an infectious disease of the skin caused by *Treponema carateum* It is characterized by an initial papular lesion of the skin followed by depigmented areas on the extremities and hyperkeratosis on the soles and palms The disease is also known as *mal del pinto azul* and *carate* Pinta is found almost entirely in the Western Hemisphere and is especially prevalent in Mexico and Colombia

Etiology *Treponema carateum* the etiologic agent of pinta is morphologically indistinguishable from *Treponema pallidum* The exact relationship of this disease to other treponematoses (syphilis yaws and bejel) has not been definitely determined and there are many similarities in the clinical manifestations of these infections Pinta is usually transmitted from person to person by direct contact It may also be spread by an insect vector

Manifestations The primary lesion of pinta appears after an incubation period of 7 to 20 days as a nonulcerative papule at the site of infection This is followed 5 to 18 months later by a secondary eruption characterized by flat erythematous and hyperpigmented lesions called *pintids* Late lesions develop after several years and appear as vitiligoid slate blue or variously colored patches of the skin The hands wrists knees and ankles are commonly involved and hyperkeratoses of the palms and soles are also seen Aortitis and spinal fluid abnormalities similar to those found in neurosyphilis have been observed in some pinta patients The Wassermann reaction of the blood and flocculation tests for syphilis are usually positive in the late stages of the disease Eosinophilia is often present

Treatment A single injection of 1 2 million units of procaine penicillin or benzathine penicillin G produces rapid disappearance of the *T carateum* from the lesions of pinta and a decline in serologic titer It is the treatment of choice in this disease and is more effective than chlortetracycline chloramphenicol or oxytetracycline

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156 LEPTOSPIRAL INFECTIONS

Paul B Beeson

Etiology and Epidemiology The leptospirae are delicate tightly coiled spirochetes many of which

make every effort to relieve these patients of their anxiety by correcting mistaken ideas regarding the infection and by emphasizing the good prognosis whenever possible His attitude toward the patient should be free of censure

Upon learning the diagnosis many patients either condemn their marital partners and threaten divorce or separation or else refuse to impart the information to their spouse The physician should not enter into the moral aspects of the disease but should make certain that the marital partners of patients with infectious syphilis are examined at regular intervals for evidence of the disease

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154 YAWS

Albert Heyman

Definition Yaws is an infectious tropical disease caused by the *Treponema pertenue* It is characterized by a primary cutaneous lesion which is followed by a granulomatous skin eruption and in some instances by late destructive lesions of the skin and bones The disease is also known as *frambesia pian bouba* and *parangi*

Etiology The etiologic agent of yaws the *T pertenue* is morphologically indistinguishable from *Treponema pallidum* it further resembles the spirochete of syphilis as it produces a positive reaction with the Wassermann and flocculation tests for syphilis and is also susceptible to arsenicals bismuth and penicillin Cross immunity between the two diseases has been observed in both man and experimental animals There has been considerable controversy as to whether the two diseases were at one time identical and have been modified over the years by climate race and other factors

Epidemiology Yaws is confined entirely to the tropics and is prevalent in the West Indies South Pacific islands equatorial Africa and South America The disease is usually acquired before puberty and is spread by direct contact with open lesions containing the spirochete Transmission of the disease occurs rarely by sexual contact Certain species of flies are also thought to be vectors of this infection The disease is more common in natives with poor personal hygiene

Manifestations Following an average incubation period of 3 to 4 weeks a primary lesion the *mother yaw* appears at the site of inoculation This is almost invariably extragenital and usually occurs on the legs This lesion is a granuloma which later ulcerates and heals with scar formation About 6 to 12 weeks after the appearance of the lesion a generalized eruption develops consisting of large papules or granulomas on the face neck extremities and buttocks These lesions often occur about the mucocutaneous junctions such as the mouth nose and rectum and resemble condylomas of secondary syphilis They heal slowly but relapses may occur months or years after the onset of the initial

mon in Weil's disease being reported in about 20 per cent of cases They usually take the form of recrudescence of fever during the second week together with muscle pain and headache The duration of fever in relapses is usually short i e 2 to 5 days Severe hepatic or renal involvement is rare during relapses

Laboratory Findings The blood leukocyte count is nearly always elevated ranging from 12 000 to 25 000 cells per cubic millimeter The platelet and prothrombin content of the blood may be reduced though seldom is either of these so reduced as to be a likely cause of the hemorrhagic tendency In the majority of cases the bilirubin content of the plasma is increased and bilirubin appears in the urine The stools are seldom acholic however Disturbed liver function may be manifested by positive cephalin flocculation and an elevated thymol turbidity reading In patients who have leptospiral nephritis there may be oliguria hematuria proteinuria and cylindruria and elevation of the blood nonprotein nitrogen Examination of the spinal fluid reveals abnormal findings in 85 to 90 per cent of cases the commonest of these being increase in number of cells—i e from 10 to 250 per cubic millimeter the majority being mononuclear Xanthochromia of the spinal fluid is usually present in patients with clinical jaundice

Differential Diagnosis Weil's disease is not difficult to recognize in its full blown form The combination of sudden onset with fever leukocytosis jaundice muscle tenderness conjunctival suffusion and pleocytosis in the spinal fluid comprises a fairly characteristic syndrome Furthermore a history of contact with water likely to be contaminated by rats is helpful It is probable however that the diagnosis is overlooked in as many as one half the cases especially those of short duration and without jaundice The statement made previously that jaundice occurs in about 70 per cent of cases should be interpreted with this in mind Recognition of Weil's disease may be difficult in cases with predominant meningeal or renal manifestations In the early stages Weil's disease may simulate such acute infectious diseases as influenza trichinosis typhus fever brucellosis and the acute bacterial meningitides Diseases with which Weil's disease in its later manifestations may be confused include infectious hepatitis obstructive and hemolytic jaundice and acute glomerulonephritis If the various manifestations of Weil's disease are known and its possible existence is considered there is rarely much difficulty in making at least a presumptive diagnosis

Laboratory Diagnosis Experienced observers often are able to find leptospirae in dark field examination of the blood during the first 5 days of the disease Inexperienced observers however are likely to make an erroneous diagnosis of leptospiral infection because strands of fibrin being whipped about by Brownian motion are readily mistaken for leptospirae The organisms may be isolated from the blood by inoculation of guinea pigs mice or hamsters during the first few days of the disease Leptospirae can also be isolated from the urine between the second and fourth weeks of disease by animal inoculation in about 25 per cent of cases Good results have been obtained in a few laboratories by cultural isolation of leptospirae from the blood or urine Specific antibodies for leptospirae appear in the blood of patients with Weil's disease during the second week and often are present in extremely high titers agglutination with serum dilution of 1 10 000 is not uncommon and even 1 1 000 000 has been reported This test gives the best results when freshly prepared antigen is employed some workers prefer to use live leptospirae Efforts are being made to prepare stable soluble antigens which will be suitable for use in ordinary hospital laboratories obviating the necessity of maintaining cultures of all strains for diagnostic tests A presumptive diagnosis of Weil's disease can be made during the first few days of the disease on the basis of a muscle biopsy since the changes found in voluntary muscle are fairly characteristic The spinal fluid should always be examined when the possibility of Weil's disease is being considered the finding of xanthochromia and pleocytosis is strong evidence in support of the diagnosis Yellow discoloration of the spinal fluid does not occur in infectious hepatitis or other forms of jaundice unless the icterus is very marked and of long duration

Treatment In Europe good therapeutic effect has been reported following the use of high titer antiserum especially when given early in the disease Such serum is not available in the United States It has been suggested that blood or plasma from persons convalescent from Weil's disease might be of similar value

In experimental infections antibiotic therapy especially with penicillin and Aureomycin has proved effective in controlling leptospiral infection Furthermore case reports suggesting beneficial effect of these antibiotics in human disease have been published Generally however the clinical results have been disappointing In one well designed clinical test carried out during a small epidemic in Puerto Rico there did not appear to be any significant curative effect from any of several antibiotics alone and in combination Nevertheless one would probably be justified in giving the patient a trial of penicillin or Aureomycin in large doses e g 5 to 20 million units of penicillin or 3 to 4 Gm Aureomycin per day

The general care of the patient is the same as in any acute systemic infection It is unlikely that

are pathogenic for man and various animals They can be cultivated in the laboratory on media containing serum or other body fluids and can produce infection in such laboratory animals as guinea pigs hamsters mice and chick embryos Of some twenty serologically differentiated strains pathogenic for man the following have been shown to cause human infection in the United States *Leptospira icterohaemorrhagiae L canicola L pomona L grippotyphosa L autumnalis* Leptospirae are parasites of a number of wild and domestic animals some of which e g rats may excrete the spirochetes in the urine over long periods of time Human beings become contaminated when swimming in stagnant pools or canals or when engaged in such occupations as ditch digging sewer work fish cleaning poultry cleaning and farming Human infection has been acquired from mice swine and dogs as well as from rats The fact that leptospirae do not readily survive exposure to cold may account for the seasonal incidence of human leptospiral infection all forms being most frequent in the summer Cases of leptospiral infection are comparatively rare in children this may be due in part to some natural immunity but is doubtless related in large measure to the occupational factors in exposure The severest clinical form—Weil s disease—is usually observed in persons above the age of thirty whereas the milder forms such as aseptic meningitis and nonspecific grippelike illness are the usual expressions of leptospiral infection in adolescents and young adults

Pathogenesis The portal of entry in infections of human beings apparently is variable Evidence indicates that leptospirae can enter the body through the digestive and respiratory tracts or through abrasions of the skin In the earliest clinical stage of infection the organisms are present in the blood as a consequence of this dissemination they later cause inflammatory changes in many parts of the body including striated muscle liver kidney eye and meninges The lesions in *muscle* consist of focal necrosis attended by a variable degree of cellular reaction the majority of the cellular elements present consist of sarcolemma nuclei while inflammatory cells are comparatively rare The absence of vascular changes in this lesion differentiates it from similar muscle lesions which may occur in the rickettsial diseases Similar changes are encountered in the myocardium The *liver* is generally enlarged and icteric The histologic picture is that of slight focal degenerative phenomena in the liver cells with some evidence of liver cell regeneration and diffuse bile stasis in the bile canaliculi *Rare instances* of extensive central and midzonal necrosis are encountered The changes in the *kidney* consist of marked degeneration of the proximal convoluted tubules which contain large amounts of proteinaceous material There is generally a striking edema of the interstitial connective tissue with occasional small foci of chronic inflammatory cell infiltration Inflammation of the *meninges* is usually of low grade intensity with a *predominantly mononuclear* pleocytosis in the spinal fluid In those cases which terminate fatally there is deep jaundice of all tissues and widespread petechial hemorrhages are encountered Leptospirae are best demonstrated in sections of kidney and liver

WEIL S DISEASE

Definition Weil s disease is an acute febrile illness characterized by fever leukocytosis muscle pains and signs of acute hepatitis and nephritis

Manifestations After an incubation period of 8 to 12 days the illness usually begins suddenly often with a chill followed by a remittent *fever* ranging between 102 and 104 F *Soon after the onset* the patient begins to suffer from *muscle pains* which are most marked in the lumbar region and in the calves of the legs Headache anorexia and nausea may be experienced *during this period* There may also be soreness of the throat and cough *Fever* usually persists for 4 to 6 days terminating by rapid lysis *Jaundice* occurs in about 70 per cent of cases usually *appearing between the third and* sixth days At this time the liver is somewhat enlarged and moderately tender Jaundice usually increases in intensity for 2 to 4 days after its appearance then subsides gradually over a period of 7 to 10 days except in those cases which terminate fatally in which the severity of jaundice may increase steadily until death Splenomegaly is not common The urine output often diminishes during the latter part of the first week and in those patients who suffer severe renal involvement there may be almost complete suppression of urine in fatal cases this is usually an important factor If recovery is to occur the urine output will gradually return to normal during the second week Marked *suffusion of the conjunctiva* is likely to be present and is a finding of some help in diagnosis particularly when the underlying sclera is icteric *Cutaneous hemorrhages* of varying size may occur in the severest cases but they are not common Scarlatiniform and morbilliform *rashes* have been described but they also are uncommon *Iridocyclitis* manifested by photophobia and circumcorneal congestion occurs in 5 to 10 per cent of patients *Signs of meningeal irritation* severe headache and stiffness of the neck may be observed at any time during the first week of the disease

Recovery is gradual Most patients are asymptomatic by the end of the second week except for a rather marked asth[illegible]

nephritis The onset is usually sudden often with chill Temperature rises to 102 to 105 F and remittent fever continues for 3 or 4 days then subsides There may be a second brief febrile episode after a free period of 1 to 3 days The chief symptoms are headache and muscle pains occasionally there is acute arthritis so that the picture simulates acute rheumatic fever Conjunctival suffusion and muscle tenderness are the chief physical findings The spleen is seldom palpably enlarged In 10 per cent of cases there is a fleeting maculopapular exanthem involving the trunk or thighs Gastrointestinal and respiratory symptoms are not prominent There is usually a moderate elevation of the leukocyte count Diagnosis can be made by demonstration of leptospiremia or by serologic tests as previously described These illnesses usually are self limited and complete recovery is to be expected

Iridocyclitis

Iridocyclitis may occur as a complication of systemic leptospiral infection either during or immediately following the other manifestations In some instances it comes on abruptly months after the other illness Under such circumstances the relationship of the ophthalmic lesion to the preceding illness may not be appreciated The course is usually benign and complete or nearly complete return of ocular function can be anticipated after 2 to 4 weeks

Acute Nephritis

Cases of leptospiral infection due to *L icterohaemorrhagiae* have been reported in which manifestations of nephritis were the outstanding feature The illnesses have had sudden onset with chills and high fever—higher than would be expected in cases of acute glomerulonephritis There have been oliguria hematuria cylindruria and azotemia Recovery has begun about the end of the second week with restoration of normal kidney function by the end of the fourth week

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157 RELAPSING FEVER

Paul B Beeson

Definition Relapsing fever is an acute infectious disease caused by spirochetes belonging to the genus *Borrelia* The outstanding clinical characteristic is a relapsing type of fever

Etiology Members of the genus *Borrelia* are slender flexible spirochetes 10 to 20 μ in length (Fig 142) They move with a corkscrewlike action *Borrelia* species are pathogenic for many rodents including rats mice and squirrels They can be cultured in media enriched with serum or blood The strain encountered most commonly in North America is *Borrelia recurrentis* In other areas *Borrelia novyi* and *Borrelia duttonii* are of clinical importance

Epidemiology and Pathogenesis Relapsing fever occurs in many parts of the world including Asia Africa Europe and South and North America Wild rodents appear to be the natural reservoirs of the infection The disease is transmitted to man by insect vectors In some parts of the world human beings are infected by the bite of ticks (*Ornithodoros*) while in other localities as in Asia the

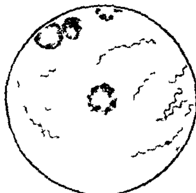


FIG 142 *Borrelia recurrentis* from blood of a man with relapsing fever (Kolle and Wassermann) (*Stitt Clough and Branham Practical Bacteriology Hematology and Parasitology* New York The Blakiston Division McGraw Hill Book Company Inc)

diet will have much influence on the course of the hepatitis Patients with oliguria should not be waterlogged with too much parenteral fluid and salt however

Prognosis The reported fatality rates refer only to the more severe cases of leptospiral infection In such cases presenting evidence of hepatitis and nephritis the fatality rate is in the range of 5 to 10 per cent

PRETIBIAL FEVER

The disease was first described by Bowdoin who studied an outbreak of 35 cases at Wrens Ga in 1940 Daniels and Grennan described a similar disease among soldiers stationed at Fort Bragg N C in 1942 It recurred at Fort Bragg in 1943 and 1944 In 1944 Tatlock isolated the etiologic agent by inoculating guinea pigs with blood from a patient First thought to be a filtrable virus this agent was later shown by Gochenour et al to be *L autumnalis* a leptospira previously known to cause human disease in Japan

Little is known regarding the pathogenesis of pretibial fever It is interesting to note that all the cases from Fort Bragg occurred in a localized segment of the reservation which was located near a small stream In addition all patients from the outbreak in Georgia had gone swimming in Brushy Creek (hence the original name of the disease *Brushy Creek fever*) The significance of these observations is not clear at present

The incubation period appears to be 10 to 15 days or longer The onset is usually sudden with frontal headache muscle pains backache post orbital pain chills or chilliness and fever About one third of the patients have a transitory sore throat and cough There may be nausea vomiting and bradycardia The fever is spiking in nature with recurrent chills It ranges between 100 and 105 F and persists for 4 to 8 days An unusual eruption appears on about the fourth day of illness in most of the patients The lesions consist of erythematous blotches with irregular margins which are raised warm and slightly tender to touch The rash characteristically involves the pretibial regions but occasionally is diffusely distributed over the entire body The eruption usually persists for only 24 to 48 hr The spleen is almost always palpable early in the disease but there is no generalized lymphadenopathy

A mild leukopenia is a feature of the disease usually appearing between the third and fifth days of illness The differential count shows no significant change The spinal fluid in three patients with stiff ness of the neck was normal

Full recovery takes place rapidly after subsidence of the fever

BENIGN ASEPTIC MENINGITIS

In young individuals leptospiral infection may take the form of an acute systemic disease dominated by signs of meningeal inflammation and without evidence of involvement of the liver or kidneys Several strains have been shown to be capable of eliciting this clinical syndrome including *L pomona L icterohaemorrhagiae L canicola* and *L sejro*

The manifestations are hardly distinguishable from those of the acute viral meningitides such as lymphocytic choriomeningitis nonparalytic polio myelitis and mumps The onset is acute with chilliness or chills malaise muscle pain headache photophobia and pain on movement of the eyeballs Fever is variable from 100 to 104 F After a day or two headache becomes more intense and there are pain and stiffness in the neck and back Examination at this time may reveal some generalized muscle tenderness and conjunctival suffusion (occasionally subconjunctival hemorrhages) together with signs of meningitis Routine laboratory tests show normal urine and blood without the leukocytosis so regularly seen in Weil s disease The spinal fluid is under slightly increased pressure its protein content is elevated to 50 to 100 mg per 100 ml its dextrose content is normal and there is a pleocytosis The cells are predominantly mononuclear rarely as many as 50 per cent may be polymorphonuclear leukocytes The total count is usually between 50 and 300 per cubic millimeter this point may be of some help in differentiation from mumps meningitis and lymphocytic choriomeningitis where the total count is often higher

The disease is self limited fever and other symptoms subside in 6 to 12 days There are no residual effects In view of the short benign course and lack of convincing evidence of benefit from antibiotic therapy the only treatment indicated is that for relief of symptoms Specific diagnosis may be achieved by the methods described in connection with Weil s disease

THE "NONSPECIFIC LEPTOSPIRAL ILLNESSES

In some parts of the world mild leptospiral illnesses are recognized fairly commonly They are usually acquired through some occupational exposure hence are designated by such names as cane field fever swamp fever" water fever" dairy grippe rice field fever etc The leptospirae associated include *L icterohaemorrhagiae L canicola L pomona L grippotyphosa L sejro L mitis* and *L bataviae*

The clinical pattern in this form of leptospiral infection has been likened to a mild form of Weil s disease with little or no evidence of hepatitis or

of the world It is recommended that two injections of this drug be given intravenously 3 to 5 days apart the dose being 0 04 Gm for adults Arsenical therapy is likely to cause a Herxheimer like reaction 4 to 12 hr after the injection evidenced by rise in temperature malaise and intensification of symptoms This reaction can cause death of the patient when superimposed at the height of a severe febrile attack Consequently it is usually recommended that specific therapy be withheld in severely ill patients until a natural crisis occurs The patient should be given supportive therapy meanwhile in the form of parenteral fluids and electrolytes Mapharsen is then administered at the onset of the next febrile period or a day or two before it is expected Further treatment is indicated in the event of a relapse

Prognosis Relapsing fever is not in itself a highly fatal infectious disease However because it occurs frequently under conditions of famine and extreme poverty and therefore may be associated with other infections and malnutrition a significant fatality rate is usually ascribed to it Reported fatality rates have varied from 2 to 50 per cent they would probably be less than 2 per cent among otherwise healthy persons given proper treatment

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158 RAT BITE FEVER—*SPIRILLUM MINUS* INFECTION

Paul B Beeson

Definition Rat bite fever is an acute infectious disease caused by *Spirillum minus* and characterized by relapsing fever arthritis and a skin eruption

Etiology The causative organism is a spirillum 2 to 5 μ in length it has two to five broad spirals and is propelled by flagella The organism is easily identified in dark field preparations by its quick darting motility It is found occasionally in the blood of apparently healthy rats mice and guinea pigs

Epidemiology In man infection by *S minus* is almost always acquired through the bite of a rat It is commonest in infants and young children but may also occur in adults Rats may attack sleeping persons and will bite anyone attempting to catch or handle them

Manifestations The incubation period varies widely from 1 to 6 weeks With the onset of symptoms the site of the rat bite usually becomes swollen tender and purplish red The regional lymph nodes also become enlarged There is fever usually relapsing A chill may occur at the onset of a febrile period Bouts of fever last 2 to 4 days and are separated by afebrile periods also lasting 2 to 4 days The principal symptoms during febrile episodes are malaise headache sweating photophobia nausea and vomiting In perhaps 50 per cent of cases there is *arthritis* with redness and swelling of one or more large joints In a similar proportion of cases a *skin eruption* occurs usually on the extremities The rash is frequently asymmetric in its distribution and most commonly consists of reddish or purplish plaques which may become large and confluent The disease tends to run a prolonged course usually 4 to 8 weeks but cases have been reported in which clinical manifestations continued for more than a year One case of subacute bacterial endocarditis due to this organism has been observed

Laboratory Findings The total leukocyte count may be normal or there may be a moderate leukocytosis In prolonged cases there is a normochromic anemia Biologic false positive serologic tests for syphilis are frequent The *S minus* seldom can be found in the blood or tissues of patients suffering from this infection and can usually be demonstrated only by transmission to laboratory animals Mice or guinea pigs may be inoculated intraperitoneally with the patient s blood The *S minus* usually can be found in the blood of the animal by dark field examination 1 to 3 weeks later Since laboratory animals may be naturally infected with *S minus* precautions must be taken to ensure that the animals used in this test are free of infection before inoculation

There are reports of isolation of this *Spirillum* from the blood by culture using routine bacteriologic blood culture technique

Differential Diagnosis It is important to inquire about rat bite in all patients with a relapsing type of fever In patients with a history of rat bite the principal problem is in differentiating between *S minus* infection and *Streptobacillus moniliformis* This cannot be done with certainty on clinical grounds but a prolonged incubation period and

principal vector is the body louse The excreta of the louse may be infectious and disease in man may follow the crushing of a louse on the skin especially when the area is scratched Fleas and bedbugs also have been suspected of transmitting relapsing fever It is likely then that under certain circumstances an animal reservoir is not necessary for perpetuation and instead that infection is transmitted from man to vector to man In the United States relapsing fever has been recognized predominantly in the West and in Texas in these areas ticks appear to be the principal vectors with wild rodents or bats as reservoirs

After inoculation into man by contact with the excreta or by the bite of an arthropod *Borrelia* is apparently disseminated by way of the blood stream and lymphatics The large number of spirochetes present in the blood of an infected person suggests that these organisms are capable of growing in the blood itself They have also been demonstrated in the cerebrospinal fluid during the acute stage of relapsing fever Autopsy in fatal cases discloses their presence in the brain spleen kidneys and liver

Manifestations It is often impossible to determine the *incubation period* in individual cases but there is epidemiologic evidence to suggest that 5 to 11 days is the usual time *Symptoms* develop abruptly with chilliness fever headache muscle aching and nonproductive cough Nausea and vomiting are common symptoms Some patients complain of paresthesias of the face and tongue The patient appears acutely ill with flushed face and injected conjunctival and pharyngeal mucous membranes At the height of the fever there may be dizziness mental cloudiness or delirium Signs of extracellular fluid deficit—dry inelastic skin and wrinkled tongue—are often present *Tenderness of the calf muscles* is a characteristic physical finding *Jaundice* occurs in a small proportion of cases usually after several days of fever A transitory erythematous rash may be observed especially about the neck and shoulders In severe cases there may be *petechiae* *Enlargement of the spleen* is observed in about half of all cases The pattern of the temperature curve is somewhat variable Usually there is an elevation to 103 to 105 F The fever may be sustained or remittent

Course of Disease The febrile bout usually persists from 4 to 15 days and then subsides spontaneously At the termination of fever there is usually profuse sweating and the temperature may fall to 96 or 97 F gradually returning to normal during the succeeding day or two A relapse is to be expected several days later with a repetition of the same series of events Unless specific therapy is administered it is usual for a patient to have three to five attacks of fever after which the disease ceases spontaneously Additional relapses may occur but the usual end result is complete cure of the infection Death from relapsing fever is usually associated with hyperpyrexia a hemorrhagic tendency and circulatory failure

Complications are not numerous Nosebleed and gastrointestinal bleeding occur in severe cases Pneumonia may be observed at the time of death Orchitis and iridocyclitis are rare complications In China an unusual frequency of *Salmonella enteritidis* septicemia has been observed in patients with relapsing fever

Laboratory Findings The leukocyte count is variable but most commonly is between 10 000 and 15 000 per cubic millimeter The spinal fluid may show increased protein content and a pleocytosis predominantly mononuclear

A *specific diagnosis* nearly always can be made during febrile periods and occasionally even during remissions by the finding of *Borrelia* in stained smears of the peripheral blood Giemsa or Wright s stain is satisfactory If the organisms cannot be found by this method mice should be inoculated intraperitoneally with the patient s blood *Borrelia* can then be found in the blood of these animals from 16 hr to 3 days later if the patient is suffering from relapsing fever

Because of the ease with which a specific diagnosis can be made from the blood smear serologic diagnostic tests are not needed It is worth noting however that false positive serologic tests for syphilis are obtained in about 10 per cent of patients with relapsing fever and that nearly all patients develop agglutinins for *Proteus* OX K

Differential Diagnosis This disease has to be differentiated from other acute infectious diseases particularly those which may be associated with a relapsing type of fever such as malaria meningococcemia and rat bite fever At the onset of the disease the picture simulates that of Weil s disease Under conditions of poverty and famine the problem of diagnosis may be increased by concurrent epidemics of typhus fever malaria and tuberculosis Fortunately a specific diagnosis of relapsing fever usually can be made simply by microscopic examination of a stained smear of blood

Treatment Initial experience with penicillin therapy was not encouraging but that may be attributed to the fact that the dosages employed were small by present standards Excellent results have been reported in small series of cases when 800 000 or more units were given per day Chlortetracycline is perhaps even more effective and appears now to be the agent of choice Dosage recommended is 2 Gm daily for 7 to 10 days

Therapy with arsenical preparations such as Mapharsen (arsenoxide) is regarded as highly effective in relapsing fever observed in some parts

of the world It is recommended that two injections of this drug be given intravenously 3 to 5 days apart the dose being 0 04 Gm for adults Arsenical therapy is likely to cause a Herxheimer like reaction 4 to 12 hr after the injection evidenced by rise in temperature malaise and intensification of symptoms This reaction can cause death of the patient when superimposed at the height of a severe febrile attack Consequently it is usually recommended that specific therapy be withheld in severely ill patients until a natural crisis occurs The patient should be given supportive therapy meanwhile in the form of parenteral fluids and electrolytes Mapharsen is then administered at the onset of the next febrile period or a day or two before it is expected Further treatment is indicated in the event of a relapse

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Epidemiology In man infection by *S minus* is almost always acquired through the bite of a rat It is commonest in infants and young children but may also occur in adults Rats may attack sleeping persons and will bite anyone attempting to catch or handle them

Manifestations The incubation period varies widely from 1 to 6 weeks With the onset of symptoms the site of the rat bite usually becomes swollen tender and purplish red The regional lymph nodes also become enlarged There is fever usually relapsing A chill may occur at the onset of a febrile period Bouts of fever last 2 to 4 days and are separated by afebrile periods also lasting 2 to 4 days The principal symptoms during febrile episodes are malaise headache sweating photophobia nausea and vomiting In perhaps 50 per cent of cases there is *arthritis* with redness and swelling of one or more large joints In a similar proportion of cases a *skin eruption* occurs usually on the extremities The rash is frequently asymmetric in its distribution and most commonly consists of reddish or purplish plaques which may become large and confluent The disease tends to run a prolonged course usually 4 to 8 weeks but cases have been reported in which clinical manifestations continued for more than a year One case of subacute bacterial endocarditis due to this organism has been observed

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There are reports of isolation of this *Spirillum* from the blood by culture using routine bacteriologic blood culture technique

Differential Diagnosis It is important to inquire about rat bite in all patients with a relapsing type of fever In patients with a history of rat bite the principal problem is in differentiating between *S minus* infection and *Streptobacillus moniliformis* This cannot be done with certainty on clinical grounds but a prolonged incubation period and

few or no manifestations of arthritis suggest a diagnosis of *S minus* infection Laboratory tests should be made for both organisms The significance of a previous rat bite may not be appreciated in cases with a long incubation period and the disease may be confused with other infections characterized by relapsing fever such as malaria, meningococcemia *Borrelia recurrentis* infection and occasionally pyogenic infection

Treatment This infection usually responds promptly to treatment with arsenical preparations such as arsenoxide (Mapharsen) or neoarsphenamine Doses appropriate to the patient s age and size and equivalent to those used in the treatment of syphilis are satisfactory The usual practice is to give two or three injections at 3 or 4 day intervals The effect of penicillin in this infection has not been determined adequately in man but the results of animal experiments are encouraging and clinical trial is warranted There are also a few reports of prompt clinical response to treatment with streptomycin and oxytetracycline

Prognosis In the absence of serious complicating illnesses rat bite fever caused by *S minus* is never fatal

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Section 12 Rickettsial Infections

159 INTRODUCTION AND PATHOLOGY

T E Woodward and J E Smadel

The rickettsial diseases of man consist of a variety of clinical entities caused by microorganisms of the family Rickettsiaceae The rickettsiae are obligate intracellular parasites about the size of bacteria and are usually seen microscopically as pleomorphic coccobacillary organisms Each of the rickettsiae pathogenic for man is capable of multiplying in one or more species of arthropod as well as in animals and man Indeed the majority of the rickettsiae are maintained in nature by a cycle which involves an insect vector and an animal reservoir and infection of man is unimportant in the cycle Q fever is a partial exception to this generalization since man usually contracts the infection via the respiratory route by inhaling rickettsiae as an aerosol derived from infected animal or tick excretions however this rickettsiosis is also maintained in nature in ticks and their animal hosts Epidemic typhus presents a number of points of dissimilarity to most of the other rickettsioses since the natural cycle of infection involves only man and the louse Moreover the agent of epidemic typhus unlike the other rickettsiae has not established a well-organized parasitic relationship which ensures its perpetuation either in its mammalian host and reservoir (man) or in its arthropod host (louse) Man frequently dies from epidemic typhus and only rarely do recovered patients serve as a suitable reservoir (i e suffer a recurrence in later years resulting in what is known as Brill s disease) and infect their body lice Furthermore the louse is relatively poorly adapted to perpetuation of the rickettsiae which induce a fatal disease in this arthropod In contrast most rickettsiae cause only a mild disease in their mammalian hosts and do not affect their arthropod host adversely indeed a number are transmitted transovarially in insects from one generation to another

The rickettsial infections of man encountered in the United States are in order of their frequency murine typhus Rocky Mountain spotted fever rickettsialpox Q fever and Brill s disease (recurrent epidemic typhus) These diseases will receive particular emphasis however students and practitioners of medicine in this generation must be familiar with infections which they may encounter in other parts of the world or which might reappear in the United States therefore some space will be devoted to epidemic typhus scrub typhus and certain of the foreign diseases of the spotted fever group

A compendium of information on the rickettsial diseases is presented in Table 93 Since each of the rickettsioses encountered in America responds therapeutically to the broad spectrum antibiotics

Tall 98 RICKETTSIAL DISEASES

D as				Nat ral y l		Tra mis t m	Serol g d gnosis	
G up	Type	Ag t	G graphic d t l t	Arthro- p d	Mammal		W l F l r t	C mple- m t fi t
Spotted f	Rocky M t potted f	*R ri k tt*	West H m p	T k	Sm ll wild rod ts d gs	T k b te	Pos t OX 19 OX	Pos t gr p d type- pec fi
	Af t k fe r	*R ori*	M d t ra l Afri					
	R k tt l	*R k*	N th Atl t t d tates R	Blood k g m t	H	M te b t	N g t e	
Typh	E d m	*R moo er*	W ld w d	Fl	S ll od ts	I f cted fl feces into b k kin	Pos t OX 19	Pos t v gr up- d type- peci fic
	Ep d	*R prow k*	W ld w d	Body l	M	I f ted l f es into l k k	Pos t v OX 19	
	B ll d as		U S A S t l d Y g sl	R p de	y m aft n typh	l tt k f	U lly n g t	
	Scr b	*R t ut g m h*	A A tral a P fi l ds	Tro b c- l d m tes	ll od t	M t b te	Pos t OX 1	Pos ti in 50% of ases
Q f		*R b rnet*	W ld w l	T k	Sm ll m m m l ttl el p g ts	I h l t of dri d f t d m t ri l	N g t	Pos t
Tre h f		*R q t*	E rope M	Body l	M n	I f ted l f es t b k k	N g t	N d bl

the table contains no mention of therapy Procedures for diagnostic isolation of the rickettsiae are omitted from the table because they generally are less useful than serologic methods and the techniques which they require are highly specialized and hazardous for laboratory personnel Information on isolation procedures may be found in text books devoted to viral and rickettsial diseases

History of the Rickettsial Diseases Of all the afflictions of mankind the rickettsial diseases particularly epidemic typhus rank among the foremost as a cause of human suffering and death Classical typhus fever undoubtedly existed during ancient times although Zinsser cites an outbreak of illness in 1013 in a monastery near Salerno Italy as the first probable recorded incidence of this disease Typhus fever through its able transmitter the body louse has always identified itself intimately with wars famines and human catastrophes of all kinds Alone it has cast a decisive vote in the outcome of many military campaigns

The record of deaths from epidemic typhus in this century in the Balkan countries and in Poland and Russia reaches astounding figures Serbia in 1915 suffered an epidemic of major proportions with 150 000 dead and a mortality rate ranging from 20 to 60 per cent Typhus ravaged Russia and eastern Poland from 1915 to 1922 infecting 30 million of the inhabitants and causing deaths estimated at 3 million

The past two decades have seen the development of amazingly satisfactory methods for the prevention and treatment of the rickettsioses of man In fact these measures have been so successful that the rickettsioses have become of minor importance in the United States and in a number of other countries Although conquered the rickettsioses have not been eliminated and they could again become rampant if the will to control them the present high standards of sanitation and the necessary industrial capacities for production of insecticides and therapeutic agents should be decreased

through war or disaster It is worthwhile to review the classical milestones representing the clinical and scientific contributions which have resulted in the understanding and conquest of the rickettsial infections

Gerhard in 1836 differentiated typhoid fever from louse borne typhus fever In 1899 Maxcy described the clinical manifestations of Rocky Mountain spotted fever In a series of studies from 1906 to 1909 Ricketts for whom the rickettsiae microorganisms are named successfully transmitted the disease to guinea pigs incriminated the wood tick as a vector and observed rickettsiae in smears prepared from the blood of man and in the tick tissues

Nicolle in 1909 reproduced typhus fever in monkeys and demonstrated transmission by the body louse Von Prowazek in 1914 and Da Rocha Lima in 1916 demonstrated small microorganisms in the tissues of lice taken from typhus patients

Brill in 1910 recognized a febrile disease in patients in New York City as examples of mild epidemic typhus unassociated with lousiness Zinsser in later years (1934) postulated that Brill s disease was a recurrent form of typhus occurring in patients during periods of stress or waning immunity Subsequent studies have essentially confirmed Zinsser s hypothesis

Weil and Felix working with typhus patients in Poland in 1915 recognized that agglutinins for certain proteus organisms appeared in the serum of convalescent patients The Weil Felix reaction although nonspecific in character affords a simple and valuable screening method for the diagnosis of certain rickettsioses

In 1926 Maxcy on purely epidemiological evidence surmised that typhus in this country had its reservoir in rodents and was transmitted to man by ticks or fleas Confirmation of Maxcy s hypothesis was obtained in Baltimore in 1930 by Dyer and others when they isolated rickettsiae from the brains of rats and shortly thereafter incriminated the flea as a vector This disease caused by *Rickettsia mooseri* and now designated endemic or murine typhus is distinct from epidemic typhus or Brill s disease

The development of suitable vaccines and specific diagnostic antigens was impeded until it was possible to prepare appreciable quantities of highly infectious rickettsial material in the laboratory The most important steps were (1) the Weigl vaccine (1930) which was a phenolized suspension of gut tissue obtained from body lice which had been injected intrarectally with the rickettsiae of epidemic typhus (2) the killed murine typhus vaccine prepared by Castaneda (1939) from lung tissues of rats injected intranasally and (3) the inactivated Rocky Mountain spotted fever vaccine obtained by Cox (1941) from infected yolk sacs of embryonated hen s eggs Each of the developments was applied in principle to other rickettsial agents but the low cost and relative simplicity of the egg techniques have led to their general use for preparation of vaccines and diagnostic antigens The specific diagnostic complement fixation tests for the rickettsial diseases now used in the United States stem directly from the pioneering work of Bengtson in Q fever and of Plotz on the spotted and typhus fevers during the early 1940s

The years of the Second World War saw many strides in the conquest of the rickettsioses perhaps greatest among these were the highly successful attacks on the insect vectors of disease The louse cide DDT proved to be ideal for control by dusting on the clothes of infested persons The epidemic at Naples during the winter of 1943 to 1944 established a milestone since it was the first to be suppressed within several weeks mainly by the use of insecticides On the other side of the world scrub typhus (mite borne typhus) was creating a major problem in military medicine in the Pacific area Here too the major contributions to successful control were concerned with application of miticidal chemicals to the person and his clothes

Specific therapy of rickettsial infections is a rather recent development Although hyperimmune rabbit serum (Topping 1939) ameliorated the course of Rocky Mountain spotted fever if given during the early stages and paraaminobenzoic acid (Yeomans 1944) was found to be effective in typhus fever the advent of broad spectrum antibiotics first chloramphenicol then Aureomycin in 1948 and later Terramycin provided the dramatic therapeutic results in each of the rickettsioses

Table 93 lists several rickettsial diseases which have not been mentioned in this historical review While important in themselves except for Q fever these have not been the subject of work which contributed broad principles applicable to the group

Pathogenesis Rickettsial diseases of man result from infection by one of two routes i e the skin or the respiratory tract Agents of the typhus and spotted fever group of rickettsiae are introduced into the skin through the bite of the infected arthropod vector Ticks and mites which transmit the spotted fevers and scrub typhus inoculate the rickettsiae directly into the dermis during feeding The louse and flea which transmit epidemic and murine typhus respectively deposit infected feces on the skin infection occurs when organisms are rubbed into the puncture wound made by the arthropod a process facilitated by scratching the itching bitten area The rickettsia of Q fever gains entry through the respiratory tract by inhalation of infected dust moreover i route

may occasionally be indicted in epidemic typhus when infection results from inhalation of dried infected louse feces

While multiplication of organisms probably takes place at the original site of entry in all instances local lesions appear with considerable regularity only in certain diseases viz the initial cutaneous lesions of scrub typhus rickettsialpox and African tick typhus and the pneumonitis which develops in about half the persons infected with Q fever Investigations have demonstrated that volunteers infected with either scrub typhus or Q fever develop rickettsemia late in the incubation period often some hours before the onset of fever Similar events probably occur in all the rickettsial diseases certainly circulating rickettsiae can be detected during the early febrile period in practically all patients Little is known about the pathogenesis of infection during the midportion of the incubation period However it is reasonable to assume that during this time in patients with typhus or spotted fever a transient low grade rickettsemia results from release of organisms multiplying at the initial site of infection and that this seeds infection in the endothelial cells of the vascular tree Vascular lesions developing at such sites could account for the pathologic changes including the rash (see following section on Pathology)

The underlying cause of the toxic febrile state which characterizes the rickettsial diseases as well as most infectious diseases remains unknown If the products of destruction of infected cells contribute to the state then fairly extensive damage is required i e more than that occurring late in the incubation period of scrub typhus when enough infected cells are destroyed to liberate appreciable numbers of rickettsiae into the circulation yet the patient remains afebrile and feels well Several rickettsial species contain type specific toxins which are lethal for mice what role these play in the toxic febrile state of patients remains unknown Cortisone suppresses the febrile response in patients but does not prevent death of mice injected with rickettsial toxins

Pathology The basic pathologic lesions in the spotted and typhus fever groups of diseases are in the small vessels The most diverse and extensive of these are found in Rocky Mountain spotted fever Here swelling proliferation and degeneration of the endothelial cells occur frequently with thrombus formation which partially or completely obliterates the lumen The muscle cells of the arteriole undergo degeneration represented by swelling and fibrinoid changes The adventitial tissues are infiltrated with mononuclear leukocytes lymphocytes and plasma cells Plate II illustrates the typical lesions found in a small vessel of the skin of a patient with spotted fever Such vascular damage is scattered in localized regions along the arteries veins and capillaries with normal architecture prevailing throughout most of the vascular bed The changes in murine epidemic and scrub typhus fevers resemble those in Rocky Mountain spotted fever as regards the endothelial swelling and the adventitial inflammatory infiltrations however thrombosis is uncommon and involvement of the musculature is rare

The vascular changes with resultant lesions in adjacent parenchymatous tissues occur throughout the vital organs but are most conspicuous in the heart lung and brain Interstitial myocarditis occurs in each member of this group of diseases but is usually most extensive in Rocky Mountain spotted fever and in scrub typhus In the brain the glial nodule is found in all members of the group but microinfarcts in the brain tissue or in the myocardium are most often observed in spotted fever The glial nodule represents a cellular response in an area adjacent to a small vascular lesion The microinfarct on the other hand constitutes anemic necrosis in an area whose supplying vessel has been occluded by the intimal reaction or thrombosis Visceral lesions in most of the other organs are similarly dependent upon the primary vascular abnormalities or are those nonspecific changes associated with severe febrile illnesses

A rickettsial pneumonitis occurs at least to some extent in many patients with spotted or typhus fever and is the characteristic pathologic change in patients with Q fever This is an interstitial pneumonitis which closely resembles that encountered in primary atypical pneumonia and viral influenzal pneumonia The process is patchy and consists macroscopically of areas of congestion and edema with gray granular consolidation Microscopically in the consolidated areas the alveoli are filled with compact fibrinocellular exudate containing lymphocytes plasma cells large mononuclear cells and erythrocytes but few if any polymorphonuclear leukocytes The alveolar epithelium is hyperplastic and the intraalveolar septa as well as the peribronchial and perivascular tissues are thickened by accumulations of leukocytes such as are found within the alveolar lumena

Rickettsiae can occasionally be observed microscopically in sections of tissue from persons dying from rickettsial diseases However special fixation of tissues special staining techniques infinite patience for work with the oil immersion objective and luck are required for success The failure to demonstrate rickettsiae in histologic section is of no diagnostic significance

Laboratory Diagnosis Diagnostic procedures which depend on isolation of the etiologic agent from blood or other clinical material are expensive time consuming and hazardous to laboratory per

Table 94 SEROLOGIC DIAGNOSIS OF RICKETTSIAL DISEASES IN THE UNITED STATES

Group	Disease	Weil Felix reaction				Complement fixation tests with type-specific antigen				
		Proteus OX	Illustrative titer		Cases with diagnostic titer	Rickettsial antigen	Illustrative titer			Cases with diagnostic titer
			10th day	20th day			10th day	20th day	30th day	
Spotted fever group	Rocky Mountain spotted fever	OX 19 OX 2	40 20	320 160	Most	*R rickettsii*	20	160	80	Most
	Rickettsialpox	OX 19 OX 2	0 0	0 0	None	*R akari*	0	64	128	Most
Typhus group	Murine typhus	OX 19 OX 2	160 10	640 40	Most	*R mooseri*	0	160	160	Most
	Brill's disease	OX 19 OX 2	20 0	320 0	Infrequent	*R prowazeki*	640	1280	320	Most
	Q fever	OX 19 OX 2	0 0	0 0	None	*R burnetii*	10	80	160	Most

sonnel Except in unusual circumstances the currently available serologic tests are adequate for laboratory confirmation of the clinical diagnosis in each of the rickettsial diseases

As in most serologic diagnostic procedures the demonstration of a rise in titer of specific antibody during convalescence is of prime importance in establishing the laboratory confirmation Table 94 summarizes the serologic results usually encountered in persons who suffer from rickettsial diseases in the United States The Weil Felix test employing *Proteus* strains OX 19 and OX 2 gives positive results in patients with spotted fever and murine typhus and negative results in those with rickettsial pox and Q fever It is useful as a screening procedure but cannot be relied upon to differentiate spotted fever from murine typhus

Complement fixation tests employing group specific rickettsial antigens provide data which clearly differentiate the most common infections i e murine typhus Rocky Mountain spotted fever and Q fever Moreover if type specific rickettsial antigens are employed it is generally possible to distinguish rickettsialpox from spotted fever and Brill's disease from murine typhus

Specific antibiotic therapy has little effect on the time of appearance of antibodies or on their ultimate titer provided treatment is begun some days after onset of the rickettsial disease However if the illness is cut short by early and vigorous treatment then antibody production may be delayed for a week or so and also the maximal titers attained may be below those illustrated in Table 94 Under these circumstances a sample of blood taken 4 to 6 weeks after onset of illness should be examined

Except for normochromic anemia which occurs in patients severely ill with rickettsial diseases there are no other distinctive alterations of the hematologic picture The white blood cell count in Rocky Mountain spotted fever rickettsialpox murine and epidemic typhus Brill's disease Q fever and others is usually within the normal range 6 000 to 10 000 per cubic millimeter Leukopenia is occasionally observed and in the presence of complications such as superimposed infections and extensive vascular lesions moderate leukocytosis occurs The differential blood count is usually normal

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160 ROCKY MOUNTAIN SPOTTED FEVER

T E Woodward and J E Smadel

Definition Rocky Mountain spotted fever an acute febrile illness caused by *Rickettsia rickettsii* is transmitted to man by ticks The disease is characterized by sudden onset with headache and chills and by fever which persists for 2 to 3 weeks A characteristic exanthem appears on the extremities and trunk about the fourth day of disease this rash like other anatomical manifestations of the disease stems from focal areas of endangiitis scattered throughout the body Delirium shock and renal failure occur in the severely ill Agglutinins for the proteus organisms and specific complement fixing antibodies appear in the patient's serum during the second or third week of disease The broad spectrum antibiotics are highly specific therapeutically A review of the pertinent historical features is given in Chap 159

Etiology and Epidemiology The causative microbe *Rickettsia rickettsii* represents the prototype for the rickettsial group of agents The minute organisms about 1 μ in length and 0 2 to 0 3 μ in width are purple when stained by Giemsa's method or red by Macchiavello's technique and often occur in pairs surrounded by a halo as if encapsulated (see Plate II) The rickettsiae grow in the nucleus as well as in the cytoplasm of infected cells of ticks mammals and embryonated eggs the intranuclear situation of the organisms is shared by the other members of the spotted fever goup but not by rickettsiae of the typhus group *Rickettsia rickettsii* are readily distinguishable from the agents of the typhus fevers by cross immunity tests in guinea pigs and by complement fixation tests employing antigens prepared from infected yolk sac tissues The differentiation of *R rickettsii* from closely related members of the spotted fever group frequently requires elaborate procedures Strains of the agent of Rocky Mountain spotted fever vary considerably in their virulence for man and animals

The first reports of spotted fever in Idaho and Montana during the final decade of the last century led to the name Rocky Mountain spotted fever However the disease is now known to occur in all states except Maine and Vermont as well as in Canada Mexico Colombia and Brazil Although related diseases are found on other continents this particular infection is limited to the Western Hemisphere About five hundred cases of spotted fever occur annually in the United States the mortality in the days before specific therapy was about 20 per cent The attack rate per unit of population is highest in Wyoming but the rates in Delaware Maryland Virginia and North Carolina are about the same as those in Montana Idaho Nevada and Utah Moreover approximately two fifths of all cases in the United States occur each year in the Middle Atlantic states just mentioned

A number of species of ticks are found infected with *R rickettsii* in nature but only two species are important in transmitting spotted fever to man These are *Dermacentor andersoni* the wood tick which is the principal vector in the West and *D variabilis* the dog tick which assumes this role in the East Ricketts almost half a century ago demonstrated that infected adult female ticks transmit the agent transovarially to at least some of their offspring Ticks which become infected either through the egg or at one of the stages during their developmental cycle by feeding on an infected mammal harbor the rickettsiae throughout their lifetime which may be as long as several years Thus the tick probably serves as a reservoir in addition to being a vector Small wild mammals are suspected of playing an important role in spreading the rickettsiae in nature by infecting those new

ticks which feed on them during that period of the disease when rickettsemia is occurring

Disease in man is generally acquired from the bite of an infected tick However transmission is unlikely unless the tick remains attached for a number of hours Infection may also be acquired through abrasions in the skin which become contaminated with infected tick feces or tissue juices hence the hazard associated with crushing ticks between the fingers when removing them from persons or animals

There are seasonal variations in the incidence of cases of spotted fever as well as differences in age and sex distribution of cases In each instance these differences are related to exposure to ticks Thus most patients are seen during the period of maximal tick activity i e late spring and early summer Topping found that about half the cases in the Western states occurred in men over forty whereas half those in the Eastern states were in children under fifteen This age distribution is undoubtedly influenced by propinquity to the wood and dog ticks respectively Mortality increases with age of the patient hence the crude fatality rates in the West are generally higher than those in the East However when corrected for age the rates in comparable groups are similar

Clinical Manifestations *Incubation Period and Prodromata* A history of tick bite is elicited in approximately 80 per cent of patients The incubation period varies between 3 and 12 days with a mean of 7 A short incubation period usually indicates a more serious infection

Onset and Symptoms In nonvaccinated persons the onset is usually abrupt with severe headache a sudden shaking rigor prostration generalized myalgic pains especially localized in the back and leg muscles nausea with occasional vomiting and fever which reaches 103 to 104 F within the first 2 days Pain in the abdominal muscles may be severe and arthralgia is not uncommon Deep muscle palpation often elicits tenderness Occasionally the debut of illness in children and adults is mild accompanied by lethargy anorexia cephalgia and low grade fever These symptoms are similar to those of many acute infectious diseases making specific diagnosis difficult during the first few days

Pyrexia Fever continues for approximately 15 to 20 days in severe cases The febrile course in children may be shorter The pyrexia is high with morning remissions that do not reach normal levels Hyperthermia of 105 F or greater is of unfavorable prognostic significance although fatalities may occur when the patient is hypothermic with concurrent vasomotor collapse Fever generally terminates by lysis over a period of several days but rarely it does so by crisis Recurrent fever is quite uncommon except in the presence of secondary pyogenic complications

The headache is generalized and excruciating and frequently more intense over the frontal area It persists throughout the first and second week of illness in untreated cases Malaise continues for the first week irritability is notable and the patient shuns distractions such as questioning and examination

Cutaneous Manifestations The rash which is present in practically all cases is the most characteristic and helpful diagnostic sign It usually appears on the *fourth* febrile day range 2 to 6 days The initial lesions are on the wrist ankles palms soles and forearms The first lesions are macular nonfixed pink irregularly defined and 2 to 6 mm in width (Plate II) A warm compress applied to the extremity accentuates the rash in the early stages The exanthem is most prominent when the temperature is elevated After 6 to 12 hr the rash extends centripetally to the axilla buttocks trunk neck and face (This is in contrast to the eruption of typhus fever which begins on the trunk and spreads centrifugally rarely involving the face palms or soles) The rash becomes maculopapular after 2 to 3 days (it may be felt by light palpation) and assumes a deeper red hue By about the fourth day it is petechial and fails to fade on pressure Not uncommonly the hemorrhagic lesions coalesce to form large ecchymotic blemishes (Plate II) these lesions tend to form over bony prominences and may ultimately slough to form indolent slow healing ulcers Patients who have had the typical rash show brownish pigmented discolorations at the site of the previous lesions for several weeks during convalescence In milder cases the rash does not become purpuric and may disappear within several days Modern antibiotic therapy may abort the early exanthem whereas the later fixed lesion fades less rapidly under specific therapy

The application of tourniquets for several minutes or the occasional taking of the blood pressure may provoke additional petechiae (Rumpel Leede phenomenon) which is further evidence of capillary abnormalities

Cardiovascular and Respiratory Features During the early stages the pulse is full and regular but accelerated in proportion to the height of the temperature and the blood pressure is well sustained During the peak of illness in seriously ill children and adults the pulse is rapid and feeble and hypotension of 90 mm Hg is common If circulatory failure is long sustained the resultant hypoxia and shock lead to agitation and delirium and contribute to the formation of ecchymoses and gangrene of fingers toes genitalia buttocks earlobes and nose Cyanosis of the peripheral ... of the body is









PLATE II

Rocky Mountain spotted fever (*Upper left*) Typical rash in a four year-old girl on the tenth day (*Upper right*) Purpuric rash in a fatal case (*Lower left*) Yolk sac smear showing intracellular *Rickettsia rickettsii* (Machiavello's stain ×1780) (*Lower right*) Biopsy from scrotum on the twelfth day showing arteriole with mural thrombus and perivascular reaction (×225)

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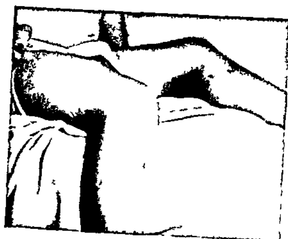
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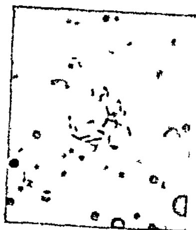
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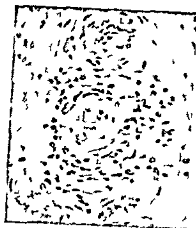


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common venous pressure determinations do not reveal elevations indicative of congestive heart failure per se nor is the venous pressure elevated following the careful administration of intravenous fluids A reduction of the total blood volume is occasionally found as are evidences of myocardial impairment as shown by electrocardiography i e low voltage of ventricular complexes minor ST segment deflections and occasionally delay in AV conduction time (Harrell) These changes are transient and similar to those encountered in patients with pneumonia typhoid fever or uremia Severely ill patients present a puffy appearance of the face hands ankles feet and lower sacrum

Respirations are either normal or slightly accelerated Cough may be harassing and nonproductive and localized pneumonitis may occur whereas pulmonary consolidation is extremely uncommon Pulmonary edema may develop particularly after the injudicious use of intravenous fluids

Hepatic and Renal Manifestations In the majority of moderately ill patients there is little alteration in the renal or hepatic function The liver may be enlarged but jaundice is unusual Oliguria commonly occurs in the seriously ill and anuria may mark the critical case Azotemia is common but when marked is a very unfavorable sign Abnormalities in liver function are probably responsible for the hypoproteinemia with reduction in the albumin fraction

Neurologic Manifestations The principal neurologic manifestations are headache restlessness and varying degrees of insomnia Stiffness of the back is common The cerebrospinal fluid is clear with normal dynamics and normal chemical constituents Coma and muscular rigidity may occur Athetoid movements convulsive seizures and hemiplegia are grave manifestations Deafness during the active stages of the disease is not uncommon As a rule all neurologic signs abate without residual Recent findings based upon follow up examinations and electroencephalograms may be interpreted as indicative of minor residual brain damage for a year or more following recovery of certain patients from Rocky Mountain spotted fever

Other Physical Manifestations Patients become dehydrated with extreme dryness of lips gums tongue and pharynx The skin is hot and dry and the conjunctivae are frequently injected and the eyes suffused Photophobia is common in the early stages of illness Petechial hemorrhages may be noted in the conjunctivae or in the retina The spleen is enlarged in approximately one half the cases and is firm and nontender Abdominal distention is frequent and occasionally some degree of intestinal ileus is observed Constipation is usual

Course of Disease In mild and moderately severe cases the disease abates within 2 weeks and convalescence is rapid In fatal cases death usually occurs during the latter part of the second week as a result of toxemia vasomotor weakness and shock or renal failure with azotemia

In vaccinated individuals who contract the disease the illness is mild with a short febrile course and an atypical rash

Complications and Prognosis If the serious manifestations of spotted fever mentioned above are regarded as intrinsic parts of the disease then complications are uncommon and consist mainly of secondary bacterial infections viz bronchopneumonia otitis media and parotitis Thrombosis of major blood vessels may result in gangrene of a portion of an extremity Hemiplegia and peripheral neuritis are important but rare sequelae

The over all mortality rate for spotted fever was formerly about 20 per cent Fatal outcome occurred in more than half of persons over forty years of age but was appreciably lower in children and young adults Since the introduction of the broad spectrum antibiotics and the development of more precise knowledge regarding correction of the physiologic abnormalities which develop during the disease deaths rarely occur from this infection even among the patients who first come under medical care rather late in the disease

Differential Diagnosis During the early stages of infection before the rash has appeared differentiation from other acute infections is difficult History of tick bite while living or traveling in a highly endemic area is helpful The rash of meningococcemia resembles Rocky Mountain spotted fever in certain aspects since it is macular or maculopapular or petechial in the chronic form and petechial confluent or ecchymotic in the fulminant type The meningococcic skin lesion is tender and develops with extreme rapidity in the fulminant form whereas the rickettsial rash occurs on about the fourth day of disease and gradually becomes petechial The exanthem of rubella rapidly becomes confluent while that of rubeola almost never becomes petechial The exanthem of varicella or variola is first erythematous and later becomes vesicular The rose spots of typhoid fever are usually on the lower chest or abdomen and remain delicate without hemorrhagic character Rocky Mountain spotted fever skin lesions in contrast to those of typhoid begin on the periphery of the body and later become petechial The rash of infectious mononucleosis is usually morbilliform on the trunk and rarely becomes petechial Angina lymphadenopathy and atypical lymphocytes in the blood are differentiating features

Murine typhus is a milder disease than Rocky

Table 95 EFFECT OF SPECIFIC ANTIBIOTICS ON THE COURSE OF THE MAJOR RICKETTSIOSES

Disease	Untreated		Treated	
	Average duration of fever days	Mortality per cent	Average duration of fever after Rx, days	Mortality per cent
Rocky Mountain spotted fever	16	21	3	0
Epidemic typhus	14	30	2	0
Murine typhus	12	2	2	0
Scrub typhus	14	15	1	0

tube and elixir of oxytetracycline containing 250 mg per ml is available Oxytetracycline hydrochloride when mixed with a sodium glycinate buffer is a stable solution suitable for intravenous administration A daily dose of 1 0 Gm suffices

Table 95 summarizes information on the duration of disease and the mortality in the major rickettsioses prior to and since the introduction of specific antibiotic therapy

Duration of Therapy and Therapeutic Response Therapy with antibiotics is continued until the toxemia has abated the general condition has markedly improved and the temperature has remained at normal levels for 24 hr In uncomplicated cases of spotted fever there is symptomatic improvement within 24 hr and normal temperature in 60 to 72 hr

Figure 143 illustrates the typical response in a moderately ill adult in whom specific therapy was augmented by a moderate supportive regimen Fig

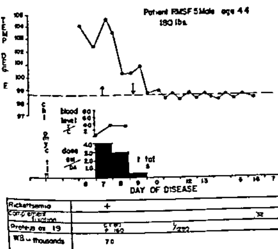


Fig. 143 Rocky Mountain spotted fever Course of illness in a moderately ill adult patient treated with chloramphenicol. Patient became afebrile in 2 5 days

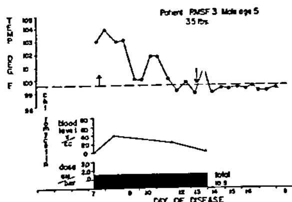


Fig 144 Rocky Mountain spotted fever Clinical course in a severely ill, semicomatose boy who received energetic supportive therapy as well as chloramphenicol. The temperature reached normal levels 6 days after treatment was instituted Convalescence was uncomplicated

ure 144 summarizes the findings in a severely ill child who required a longer course of antibiotic treatment as well as vigorous supportive care

Supportive Care *Nursing Care* Frequent turning of the patient relieves pressure from prominent bony parts such as the lower spine hip elbows and heels thereby lessening superficial skin lesions In comatose patients frequent turning also militates against the development of hypostatic pneumonia Proper mouth hygiene with frequent swabbing of the oral cavity may avert the development of parotitis and gingivitis Sucking of the juice of a lemon or the oral use of glycerin or mineral oil is helpful

Protein Balance A generous intake of protein should be provided by frequent feedings as soon as the disease is suspected in order to avoid subsequent protein deficiency Usually food is well tolerated by patients with rickettsial disease and the daily diet should provide from 3 to 5 Gm protein per kg normal body weight, with adequate carbohydrate and fat to make it palatable When the patient is uncooperative the diet may be supplemented by hourly liquid protein feedings via stomach tube

At the critical stage when hypoproteinemia is present and changes in capillary permeability lead to edema and vascular embarrassment, careful attention is given to the parenteral administration of protein supplements When indicated by hematologic studies whole-blood transfusions given slowly are helpful or if the total red cell mass is adequate one of the preformed protein supplements is bene-

Mountain spotted fever the rash is less extensive nonpurpuric nonconfluent and renal and vascular complications are uncommon Not infrequently differentiation of these two rickettsial infections must await the results of specific serological tests Epidemic typhus fever is capable of causing all the pronounced clinical physiologic and anatomic alterations seen in patients with Rocky Mountain spotted fever i e hypotension peripheral vascular failure cyanosis skin necrosis and gangrene of digits renal failure with azotemia and neurological manifestations However the rash of classical typhus is noted initially in the axillary folds and on the trunk and later extends peripherally rarely involving the palms soles or face The serologic patterns in these two diseases are distinctive when specific rickettsial antigens are employed in tests Moreover louse borne typhus is not recognized in the United States except in the form of Brill s disease (recurrent typhus fever) Rickettsialpox although caused by a member of the spotted fever group of organisms is usually readily differentiated from Rocky Mountain spotted fever by the initial lesion the relative mildness of the illness and the early vesiculation of the maculopapular rash The Weil Felix reaction is positive in Rocky Mountain spotted fever and in murine and epidemic typhus but is negative in rickettsialpox Agglutinins against *Proteus* OX 19 and OX 2 appear in the serum of patients with spotted fever but only those against OX 19 are found in murine and epidemic typhus

Therapy

General Certain physiochemical changes occurring in the patient seriously ill with one of the diseases of the typhus spotted fever group should be understood before outlining a therapeutic regime These changes are circulatory collapse coma oliguria and anuria azotemia anemia hypoproteinemia hypochloremia and edema of the underlying tissues These alterations are often absent in the mildly ill and in them management is much less complicated The therapeutic principles necessary for the treatment of all rickettsioses are (1) specific chemotherapy and (2) supportive care Attention to both is mandatory for the seriously ill patient first recognized late in the disease Contrariwise during the first week and in the moderately ill patient supportive therapy may be less energetic since specific chemotherapy usually suffices The early mild case may be successfully treated at home whereas the later case should receive hospital care

Therapeutic measures advisable for the management of Rocky Mountain spotted fever will be described in detail Variations of this regimen which apply to the other rickettsioses are described in subsections relegated to other diseases of the typhus-spotted fever group and Q fever

Specific Therapy Specific therapy is most effective when initiated during the early stages of disease coincident with the appearance of the rash When therapy is delayed until the rash has become hemorrhagic and widespread the response is less dramatic The antibiotics of choice are chloramphenicol chlortetracycline and oxytetracycline which are effective because of their rickettsiostatic properties They are not rickettsiocidal Each of the antibiotics is supplied for oral and intravenous use

Chloramphenicol (*Chloromycetin*) The initial oral dose is calculated on the basis of 50 mg per kg body weight and subsequent doses of 1 0 Gm are given every 8 hr or 0 5 Gm every 4 hr for adults Daily requirement for children is calculated on the basis of 75 mg per kg body weight per day Chloromycetin hydrochloride available in 0 5 Gm ampuls may be given intravenously on a schedule of 0 5 Gm every 6 hr to adults This solution is incorporated in either 5 per cent glucose or in physiologic saline in volumes not exceeding 200 ml The direct intravenous administration of the undiluted suspension is not advised Chloramphenicol powder obtained from the gelatin sealed capsules may be suspended in saline or distilled water for administration via stomach tube Chloromycetin palmitate a palatable liquid preparation suitable for children may be given for maintenance therapy calculated on the basis of 100 mg per kg body weight per day divided in equal doses at 6 to 8 hr intervals

Chlortetracycline The initial oral dose is calculated on the basis of 25 mg per kg body weight Subsequent daily doses of 25 mg per kg body weight are divided equally and given at 4 to 6 hr intervals The 4 hr schedule reduces the tendency to nausea and the concurrent administration of milk or semisolid nourishment is desirable Chlortetracycline hydrochloride with a sodium glycinate buffer is prepared in 100 mg vials for intravenous therapy It is administered on the basis of 5 to 10 mg per kg body weight per day divided in equal doses at 6 hr intervals although 100 mg every 6 hr usually suffices The buffered antibiotic is dissolved in 10 ml of sterile water or physiologic saline for intravenous administration Care should be exercised in preventing perivascular extravasation and the chemical phlebitis that might result

Oxytetracycline The initial oral dose is calculated on the basis of 25 mg per kg body weight Subsequent daily doses of 25 mg per kg body weight are given at intervals of 4 to 6 hr Children require doses of 25 to 50 mg per kg body weight per day Oxytetracycline powder may be suspended in distilled water for administration by stomach

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161 RICKETTSIALPOX

T E Woodward and J E Smadel

Definition Rickettsialpox is a mild nonfatal self limited acute febrile illness caused by *Rickettsia akari* which is transmitted from mouse to man by mites It is characterized by an initial skin lesion at the site of the mite bite a weeks febrile course and a papulovesicular rash

Etiology and Epidemiology Rickettsialpox was first recognized in New York City in 1946 and later in several areas in New England It has an annual incidence of approximately 200 cases The vector is a small colorless mite *Allodermanyssus sanguineus* (Hirst) which infests small mice and rodents House mice serve as the reservoir of infection

Rickettsia akari is morphologically and biologically similar to other rickettsiae and is antigenically related to but distinct from *R rickettsii* the cause of Rocky Mountain spotted fever Mice guinea pigs and fertile hens eggs are susceptible to experimental infection and diagnostic antigens prepared from infected yolk sacs are used in complement fixation tests

Clinical Manifestations The initial skin lesion appears about 7 to 10 days after the mite bite as a firm red papule 1 to 1 5 cm in diameter In a few days the center vesiculates and the papule is surrounded by an area of erythema The regional lymph glands are moderately enlarged The primary lesion which is never painful becomes covered with a black scab it heals slowly and a small scar is visible on separation of the crust

The febrile phase begins 3 to 7 days following the initial lesion and a body exanthem may accompany the fever or begin several days later The onset of fever is sudden with chilly sensations or frank chills headache sweats myalgia anorexia and photophobia The pyrexia ranges from 103 to 104 F and continues for about a week occasionally with morning remissions

The exanthem is maculopapular vesicular generalized in distribution and may be abundant or scant The lesions may involve the oral cavity but not the palms or soles In a week the vesicles dry and form scabs which eventually scale but leave no scar

The constitutional symptoms are generally mild and the course of illness uncomplicated No fatal cases have been reported

The disease may be confused with varicella (chickenpox) which is different in that it occurs usually in childhood and has no initial lesion and the papular cutaneous lesion is entirely transformed into a vesicle Variola (smallpox) is accompanied by a more severe constitutional reaction and the vesicles become pustules The skin lesions of the other rickettsioses differ in their lack of vesiculation The Weil Felix reaction remains negative in this rickettsial disease but the specific complement fixation test is a useful laboratory diagnostic aid even though there is considerable crossing with materials from Rocky Mountain spotted fever

Treatment and Prevention Chloramphenicol chlortetracycline and oxytetracycline are all effective for treating patients with rickettsialpox The temperature reaches normal levels in about 2 days and recovery is rapid The therapeutic procedures are comparable to those used in spotted fever which are described in detail on p 1028

Control measures should be directed toward elimination of house mice and the vector mites responsible for transmitting the disease

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ficial Intravenous albumin may be particularly useful since it also aids in the reduction of tissue edema The judicious administration of one of the plasma expanders at this stage may have a definite favorable effect upon the impending circulatory collapse If the patient is anuric and azotemia is pronounced overloading the circulation with protein supplements and fluids is to be avoided The *type and amount of parenteral therapy should be* governed entirely by clinical judgment and very careful laboratory studies Frequent determinations of hemoglobin hematocrit electrolytes and protein sometimes at intervals of a few hours during crucial periods are necessary in order to ascertain abnormalities and to permit institution of corrective measures

Fluid Balance Special attention should be given to the total daily fluid requirement In the presence of coma 3 to 5 liters of parenteral fluids may be required particularly in severely dehydrated patients Using the laboratory results as a guide intravenous physiologic saline may be used to correct the hypochloremia As a rule the proper administration of intravenous saline and glucose infusions will correct the electrolytic imbalance Efforts should be directed toward ensuring a daily urinary output of approximately 1 500 ml Too rapid administration of intravenous fluids may provoke additional tissue edema and greatly increase the load upon a weakened myocardium

Complications

Pyogenic complications including otitis media and parotitis are encountered in patients severely ill with Rocky Mountain spotted fever and other rickettsioses These localized infections respond to therapy with the broad spectrum antibiotics when combined with ordinary supplemental surgical *measures The sulfonamides are unnecessary* for treatment of pyogenic complications and actually exert a detrimental effect upon the course of rickettsial infections

Pneumonitis usually develops as a result of specific rickettsial action The sputum is scant but should be examined to determine whether superimposed infection is present Specific therapy is guided by the results of these laboratory studies The pneumonitis generally responds to the antibiotic therapy already outlined and penicillin or supplemental antibiotics are rarely required for secondary bacterial pneumonia

Circulatory failure of peripheral or central origin is combatted by careful administration of elec*trolytic and protein supplements as described* Myocardial failure may develop as a result of overzealous intravenous alimentation and is recognized by the common signs of rapid pulse gallop rhythm increase in venous pressure and muffled cardiac sounds This *complication under present regimens* is unusual When the clinical signs reveal unmistakable evidence of cardiac failure digitalis may be employed in the usual manner Oxygen therapy by nasal tube mask or tent improves the cardiac and circulatory status and is helpful in hypoxic patients with involvement of the central nervous system

Prevention

Prevention is attained primarily by avoidance of tick infested areas When this is impractical personal prophylactic measures include (1) the wearing of clothing which interferes with attachment of ticks i e boots and a one-piece outer garment preferably impregnated with one of the tick repellents such as N n butyl acetanilide and (2) daily inspection of the entire body including the hairy parts to detect and remove attached ticks In removing attached ticks great care should be taken to avoid crushing the arthropod with resultant contamination of the bite wound touching the tick with gasoline or whiskey encourages detachment but gentle traction with tweezers applied close to the mouth parts may be necessary the skin area should be disinfected with soap and water or other antiseptics Similarly precautions should be employed in removing engorged ticks from dogs and other animals since infection through minor abrasions on the hands is possible Vaccines containing *R rickettsii* are available commercially and *should* be used *for those exposed to great risk* viz persons frequenting highly endemic areas and laboratory workers exposed to the agent Since the broad spectrum antibiotics were shown to be such excellent therapeutic agents in spotted fever there has been less impetus for vaccination of persons who run only a minor risk of infection

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a toxic factor which is lethal to mice and rats and may be neutralized by convalescent serum from man or lower animals

The common vector of *R mooseri* for rats and man is the rat flea (*Xenopsylla cheopis*) Blanc is of the opinion that infection may be spread from man to man by the pest flea (*Pulex irritans*) In nature the rat louse (*Polyplax spinulosis*) may transmit the agent among rodents Customarily rat fleas become infected on ingestion of blood from diseased rats the rickettsiae multiply within the intestinal cells of the arthropod and are excreted in the feces Infection in man occurs following the flea bite and contamination of the broken skin by rickettsia laden feces Dried flea feces may infect via the conjunctivae or upper respiratory tract

Rats and mice are naturally infected with murine typhus and although the rodent disease is nonfatal viable rickettsiae persist in the brain for variable periods

Murine typhus is one of the most benign and widespread of the rickettsioses in the United States Prevalent in the Southeastern and Gulf Coast states it has been identified in most of the other states and in harbor centers throughout the world wherever rats and fleas abound Through control of rats and their fleas a sharp decline in incidence has occurred since 1951 particularly in the Southern United States In urban areas the disease is more prevalent during the summer and fall months and occurs predominantly among persons working in proximity to granaries or food depots Recently there has been an extension to certain rural areas because changing agricultural practices have provided rats with ready access to adequate food supplies

Clinical Manifestations *Incubation Period and Prodromata* Based upon experimental observations the incubation period ranges from 8 to 16 days with a mean of 10 Common prodromata are headache backache arthralgia and chilly sensations Nausea malaise and insufficient temperature rises may actually precede the true onset of disease

Onset and General Symptoms A frank shaking chill and often repeated rigors are present at onset associated with a severe frontal headache and fever This triad of headache chill and pyrexia is usually followed within a few hours by nausea and vomiting Prostration malaise and weakness are sufficient to enforce cessation of activity in adults in contrast to children whose illness is less severe Occasionally mild symptoms make it difficult to define the actual onset

Pyrexia The usual febrile course in murine typhus lasts for about 12 days in adults and the temperature ranges from 102 to 104 F but may reach 105 to 106 F in children The temperature may reach high levels abruptly after onset or ascend in a stepwise manner during the first few days With the appearance of the rash fever is usually sustained with partial daily remissions which occasionally reach normal levels in the morning Defervescence is generally by lysis over several days but sometimes occurs by abrupt crisis Transient mild fever of 100 F is not uncommon during early convalescence A few patients experience only low grade fever throughout but this does not necessarily connote a mild illness

Cutaneous Manifestations The early lesions which are sparse and discrete are hidden in the axillae and inner surface of the arm Most patients then develop with surprising suddenness a generalized dull red macular rash of the upper abdomen shoulders chest arms and thighs The individual lesions are discrete and pea size with an ill defined border and fade on pressure during the first 24 hr They later become maculopapular in contrast to the exanthem of epidemic typhus which is persistently macular The distribution over the trunk with sparse involvement of the extremities palms soles and face differs from the peripheral distribution and facial involvement of Rocky Mountain spotted fever The murine rash generally appears initially on the fifth febrile day but rarely is it seen concurrently with the onset or developing as late as the seventh day

Eighty per cent of patients develop a rash which usually persists for 4 to 8 days and fades before defervescence The cutaneous manifestations vary greatly in intensity and duration and may be fleeting They are readily overlooked in dark skinned patients in whom they should be searched for by light palpation and indirect lighting

Cardiovascular and Respiratory Features An irritating nonproductive cough is frequent and is occasionally associated with moderate hemoptysis Early in the second week rales may be detected in the basilar lung areas These changes are generally rickettsial rather than bacterial in origin and respond to the broad spectrum antibiotics but not to penicillin or sulfonamide therapy Pulmonary congestion occurs in extremely ill and elderly patients

Accelerated pulse hypotension and general circulatory weakness occur in this disease although less frequently than in patients with the more severe epidemic typhus or Rocky Mountain spotted fever The reader is referred to the chapter on Rocky Mountain spotted fever (Chap 160) relative to the details of the cardiovascular features

Neurologic Manifestations Headache is the most common neurologic manifestation of murine typhus and may dominate the clinical picture It is frontally localized and continues into the second week of illness In the early stages the facial expression is strained and the patient resents distraction Stupor

162 AFRICAN TICK BORNE FEVER

T E Woodward and J F Smadel

Definition African tick borne fever also called *boutonneuse fever South African tick bite fever* is a mild to moderately severe nonfatal illness characterized by an initial lesion (called the *tache noir* in boutonneuse fever) fever of several days to 2 weeks and a generalized maculopapular erythematous rash which appears on about the fifth day and usually involves the palms and soles Specific complement fixing antibodies appear in the patient s serum during convalescence but agglutinins to *Proteus* OX 19 (Weil Felix reaction) are frequently found only in low titer

Etiology and Epidemiology The causative agent *Rickettsia conorii* is a member of the spotted fever group of rickettsiae and is transmitted to man by infected ticks In the Mediterranean area the bite of infected *Rhipicephalus sanguineus* the brown dog tick is responsible whereas in South Africa a number of ticks are assumed to be vectors viz *Haemaphysalis leachi Amblyomma hebraeum Rhipicephalus appendiculatus Boophilus decoloratus* and *Hyalomma aegyptium*

The disease occurs in the Mediterranean and Black Sea area and in Africa but not in the Western Hemisphere It is more prevalent during summer months in temperate zones whereas it occurs throughout the year in the tropics

Clinical Manifestations The clinical course is usually milder than in spotted fever with a shorter febrile period and fewer severe complications Fatalities are few and generally limited to the aged or debilitated The initial lesion heals slowly and the regional lymph nodes are enlarged The rash usually remains papular and rarely becomes hemorrhagic as it does in spotted fever

Treatment and Prevention Chloramphenicol chlortetracycline and oxytetracycline are equally effective therapeutic agents for African tick borne fever Patients generally become afebrile after two days of treatment and recovery is rapid The therapeutic procedures are comparable to those used in spotted fever which are described in detail on p 1028

The major effective methods of control are concerned with avoidance of tick bites these include application of newer repellents and prompt removal of attached ticks Effective vaccines are not available commercially

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163 MURINE (ENDEMIC) TYPHUS FEVER

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Definition Murine typhus fever is an acute specific febrile disease caused by *Rickettsia mooseri* and transmitted to man by fleas The clinical illness is characterized by fever of 9 to 14 days headache a maculopapular rash appearing on the third to fifth day myalgia moderate neurologic manifestations and the appearance during convalescence of agglutinins for certain strains of *Proteus* bacteria (Weil Felix reaction) and of specific complement fixing antibodies which react with the causal rickettsiae Treatment with the broad spectrum antibiotics is highly efficacious

Etiology and Epidemiology *Rickettsia mooseri* resembles other rickettsiae as regards morphologic properties staining characteristics and intracellular parasitism Under the electron microscope *R mooseri* contains dense masses of nuclear material in a less dense homogeneous protoplasmic substance the whole of which is surrounded by a limiting membrane It differs from *R rickettsii* in that it always multiplies within the cytoplasm of cells in contrast to the intranuclear and cytoplasmic positions of spotted fever rickettsiae

Invasion of the body by *R mooseri* provokes specific and nonspecific immunologic responses Utilizing highly purified antigens specific antibodies may be demonstrated readily by complement fixation and agglutination reactions The positive Weil Felix reaction which occurs in this disease is essentially nonspecific since it is attributable to the presence of a common carbohydrate antigen in *Proteus* OX 19 and *R mooseri* and since the reaction is also positive in epidemic typhus and spotted fever A number of investigators have demonstrated group specific rickettsial antigens common to both *R mooseri* and *R prowazeki* viz a heat stable complement fixing substance Furthermore both murine and epidemic rickettsiae possess

ing antibodies in convalescence The broad spectrum antibiotics are specific therapeutic agents

Etiology and Epidemiology The causative microbe *R prowazeki* is closely related to *R mooseri* which causes murine typhus indeed the two have a number of common antigens *Rickettsia prowazeki* was the first of the rickettsiae shown to have its own enzyme system which permits it to respire independently of the host cell (Bovarnick and Snyder 1949)

Man generally is infected when rickettsia laden louse feces are rubbed into the broken skin scratching the louse bite facilitates this process *Pediculus humanus corporis* which is peculiarly adapted to man is the only important vector of epidemic typhus It dies of its infection and fails to transmit rickettsiae to its offspring There is no known animal habitat of *R prowazeki* it is maintained by a cycle involving man louse man New epidemics apparently originate from patients with Brill s disease (recurrent epidemic typhus) Inhalation of dust containing dried louse feces may rarely cause infection

Epidemic typhus if uncontrolled behaves as a cyclic disease in a susceptible population extending over a 3 year period During the first year there is a gradual seeding of cases throughout the group during the second there is epidemic spread and during the third the epidemic tapers off because the majority of persons have already become immune Outbreaks of epidemic typhus last occurred in the United States in the nineteenth century and its presence is now recognized only in the form of Brill s disease (see p 1036)

Clinical Manifestations A classic clinical description of Old World typhus is provided in Wolbach Todd and Palfrey s monograph of 1922 Epidemic typhus resembles murine typhus but is more severe After an incubation period of about 7 days an abrupt onset of headache chill and rapidly mounting fever ushers in the illness Cephalgia malaise and prostration continue unabated until the rash appears on the fifth febrile day It is initially macular in the axillary folds but ultimately invades the trunk and extremities as a pink irregular macular lesion which becomes fixed petechial and confluent in the later stages

Neurologic features range from headache and general spasticity to extreme agitation stupor and coma Circulatory disturbances consisting of tachycardia hypotension and cyanosis are more profound than those observed in murine typhus and are almost as severe as in Rocky Mountain spotted fever Ultimately in untreated cases azotemia often reaches high levels as a result of vascular and renal failure and death occurs late in the second week of illness Furthermore thrombosis of major blood vessels and cutaneous gangrene develop in a manner similar to that seen in the virulent form of Rocky Mountain spotted fever

The complications and sequelae in epidemic typhus are more severe than those in murine typhus but not as severe as those in Rocky Mountain spotted fever However during certain outbreaks epidemic typhus was fatal to 60 per cent of those infected and convalescence in survivors was prolonged Broad spectrum antibiotics have essentially *eradicated mortality in this dread disease provided* therapy is instituted before irreversible changes have been established in the tissues

Differential Diagnosis Differentiation of epidemic typhus from the various rickettsioses and other diseases with which it may be confused is described in Chap 160 Rocky Mountain Spotted Fever The disease in epidemic form never occurs in the absence of lousiness in the general population Under the conditions in which typhus epidemics are likely to occur other diseases which may cause confusion include malaria relapsing fever pneumonia and tuberculosis Classic typhus contracted by a previously vaccinated person is usually mild and may be clinically indistinguishable from murine typhus except by serologic methods

Treatment and Prevention Chloramphenicol chlortetracycline and oxytetracycline have each been found to be highly efficient therapeutic agents in epidemic typhus Usually the patient becomes afebrile after 2 days of treatment The therapeutic procedures are comparable to those used in spotted fever which are described in detail on p 1028

The most effective measures for controlling epidemic typhus are those which eliminate lousiness DDT with its long lasting effect when dusted into clothing is ideal for this purpose In certain areas e g Korea where DDT resistant lice are found lindane powder is effective

A commercially available vaccine prepared from formalin treated infected yolk sac tissue is an effective immunizing agent

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and prostration may occur in the second week and in severe cases there may be muttering delirium and extreme agitation and coma similar to the more severe louse borne typhus Coma in elderly patients after two weeks of illness presages death Nuchal rigidity and general spasticity often suggest meningitis although the spinal fluid is essentially normal except for slight increases in pressure and lymphocytes (5 to 30 per cu mm) Transient partial deafness occurs occasionally in murine typhus patients but rarely is there localized neuritis or hemiplegia Neurologic sequelae are unusual Children experience minimal neurologic changes

Other Physical Manifestations During the first two days of illness the patient may be nauseated and vomit but vomiting later in the illness should arouse suspicion of an intercurrent complication Abdominal pain particularly in dehydrated patients is bothersome and when associated with diarrhea responds to intravenous alimentation A sluggish constipated bowel is occasionally observed Hepatomegaly and jaundice are unusual There is splenomegaly in approximately 25 per cent of patients

Photophobia retroocular pain suffusion of the eyes and congestion of the conjunctivae are common manifestations but are less severe than in the other typhus and spotted fevers Dehydrated patients often have a furred brown tongue and crusting of the gums and mucous membranes

Renal function is usually unaltered except in elderly patients with prolonged hypotension and vascular weakness Under these circumstances in seriously ill patients azotemia may develop to the degree observed in epidemic typhus The blood chlorides are low in severe murine typhus as in the epidemic type hypochloremia of 80 mEq per liter may be observed Hypoproteinemia resulting from lowered serum albumin is encountered

Course of Disease and Complications After defervescence murine typhus patients recover rapidly Fatalities occur between the ninth and twelfth days in elderly or debilitated patients usually as a result of circulatory and renal failure thrombosed blood vessels or intercurrent infection

Complications are usually pyogenic such as otitis media and parotitis and a superimposed pneumonitis may be difficult to differentiate from pulmonary congestion Fortunately the average course of murine typhus fever is uncomplicated

Prognosis The mortality in murine typhus was low even before the introduction of modern specific therapy Only one death occurred in the 114 cases studied by Maxcy and none in the 180 reported by Stewart and Pullen

Differential Diagnosis See the discussion in the chapter on Rocky Mountain spotted fever (p 1027) The geographic and seasonal occurrence of murine typhus and spotted fever differ and may help in diagnosis

Treatment and Prevention The therapeutic procedures are comparable to those used in spotted fever which are described in detail on p 1028 Chloramphenicol chlortetracycline and oxytetracycline promptly control the disease

Prevention of murine typhus in man is attained by reducing the natural reservoir and vector by applying measures for eliminating rodents and employing DDT in rat infested areas to control fleas

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164 EPIDEMIC (LOUSE BORNE) TYPHUS FEVER

T E Woodward and J E Smadel

Definition The classical epidemic form of typhus is a severe acute febrile disease caused by *Rickettsia prowazeki* and transmitted to man by the body louse Intense headache continuous pyrexia of about 2 weeks a macular skin eruption appearing on about the fifth febrile day malaise and vascular and neurologic disturbances represent the principal clinical features Confirmation of the diagnosis is made by demonstration of *Proteus* OX 19 agglutinins and of specific complement fix

modern therapeutic methods deaths are extremely rare and convalescence is short

Differential Diagnosis Scrub typhus is to be differentiated from the other members of the typhus and the spotted fever group of diseases as well as from measles typhoid fever and meningococcal infections (see Chap 160 Rocky Mountain Spotted Fever) The geographic localization of scrub typhus the primary lesion and the occurrence of OXK agglutinins are especially useful in establishing the diagnosis

Treatment and Prevention Chloramphenicol chlortetracycline and oxytetracycline are valuable specific therapeutic agents in scrub typhus The therapeutic procedures are comparable to those used in spotted fever which are described in detail on p 1028 In fact scrub typhus is more amenable to drugs than are the other rickettsial infections since patients with this disease regularly become afebrile within 24 to 36 hr after beginning treatment irrespective of the stage of disease

Prevention of disease in the individual is accomplished by the application of miticidal chemicals (dibutyl phthalate benzyl benzoate and others) to clothing and the skin There is no satisfactory vaccine

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167 Q FEVER

T E Woodward and J E Smadel

Definition Q fever is an acute infectious disease caused by *Rickettsia burnetii* and characterized by a sudden onset of fever malaise headache weakness anorexia and usually an interstitial pneumonitis Rickettsemia occurs during the febrile period and specific complement fixing antibodies are present during convalescence In contrast to the other rickettsioses the disease is not associated with a cutaneous exanthem or agglutinins for the proteus bacteria (Weil Felix reaction)

Etiology and Epidemiology *Rickettsia burnetii* (Derrick 1939) possesses the general properties of other rickettsiae but is somewhat more resistant to inactivation in unfavorable environments and more pleomorphic than the others Its infectivity after drying under natural conditions is of importance in the spread of infection to man Its pleomorphism which ranges from diplobacillary structures measuring 1 5 μ in length to tiny spheres about 0 2 μ in diameter contributes to its filterability through Berkefeld N candles This filterability led Cox (1939) to suggest the name *R diaporica* for the first American isolate but the name was subsequently abandoned when this agent was found to be identical with that causing Q fever in Australia *R burnetii* has a wide host range in nature but guinea pigs and embryonated eggs are the common laboratory hosts employed for its propagation

Human cases of Q fever are contracted by inhalation of infected dusts by handling infected materials and by drinking milk contaminated with *R burnetii* The disease in Australia is enzootic in animals especially bandicoots and is transmitted in nature by ticks Rickettsia laden tick feces may contaminate cattle hides and inhalation of such material has caused infection in man In the United States a number of species of ticks are naturally infected among them *Dermacentor andersoni* and *Amblyomma americanum* and in North Africa transovarial transmission of the agent in indigenous ticks has been demonstrated by Blanc Sheep goats and cows have been found naturally infected in Western United States and in Mediterranean areas and *R burnetii* has been recovered from the milk of such animals (Huebner et al 1948 Caminopetros 1948) Such milk as well as infected excretions from livestock probably accounts for certain

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165 BRILL'S DISEASE (RECRUDESCENT TYPHUS)

T E Woodward and J E Smadel

Definition Brill s disease is a recrudescent episode of epidemic typhus fever which occurs years after the initial attack Nathan Brill in 1898 observed a sporadic disease which resembled typhus fever among nonlousy inhabitants of New York City Zinsser in 1934 suggested on the basis of epidemiologic and immunologic considerations that this malady was a recurrent form of typhus encountered in persons who had recovered from the epidemic disease while residing in countries where it was prevalent Additional information has gradually accumulated in support of this hypothesis and recently Murray and Snyder (1951) have been successful in regularly isolating rickettsiae indistinguishable from *Rickettsia prowazeki* in lice fed on patients during the active stages of illness

Clinical Manifestations The clinical entity not always mild resembles epidemic typhus fever as pertains to character of the rash circulatory disturbances hepatic renal and nervous system changes Recovery is the rule The Weil Felix reaction with the various *Proteus* antigens is usually negative or positive in very low titer in Brill s disease The specific complement fixation reaction is valuable in establishing the diagnosis The therapeutic procedures are comparable to those used in spotted fever which are described in detail on p 1028

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166 SCRUB TYPHUS

T E Woodward and J E Smadel

Definition Scrub typhus is limited to eastern and southeastern Asia northern Australia and the adjacent islands It is caused by *Rickettsia tsutsugamushi* and characterized by a primary lesion at the site of the bite of an infected mite a fever of about 2 weeks duration a cutaneous rash which develops about the fifth day and the appearance late in the second week of agglutinins against the OX K strain of *Proteus* bacillus The broad spectrum antibiotics are specific therapeutic agents

Etiology The agent of scrub typhus resembles other rickettsiae in its physical properties but differs from them in antigenic structure vector and reservoir The disease is transmitted by larvae of several species of mites especially *Trombicula akamushi* and *T deliensis* These tiny chiggers attach themselves to the skin and during the process of obtaining a meal of tissue juice may acquire infection from the host or transmit rickettsiae to the vertebrate The infection is maintained in nature by a cycle involving mites and small rodents and by transovarial transmission in mites human infection represents an accident attributable to propinquity

Clinical Manifestations About 10 to 12 days after infection illness begins abruptly with chilliness severe headache fever conjunctival injection and moderate generalized lymphadenopathy which is most prominent in the nodes draining the area of the primary lesion The initial lesion at the beginning of fever is evidenced by an erythematous indurated area 1 cm in diameter surmounted by a multiloculated vesicle within a few days the vesicle ulcerates and becomes covered with a black crust

Fever increases progressively during the first week generally reaching 104 to 105 F but the pulse remains relatively slow i e 70 to 100 per min The red macular rash which begins on the trunk about the fifth day and spreads to the extremities sometimes becomes maculopapular but usually fades in a few days The course of the disease and the complications resemble those of endemic and epidemic typhus however interstitial myocarditis is more prominent than in the other typhus fevers

Prognosis Prior to the introduction of the broad spectrum antibiotics the mortality varied from 1 to 60 per cent depending on the geographic area and the virulence of the local strains of *R tsutsugamushi* and convalescence was prolonged With

Section 13 Viral Infections of the Respiratory Tract

168 COMMON RESPIRATORY DISEASE

A E Feller

The acute respiratory infections may be considered for purposes of discussion as a spectrum of clinical conditions with gradations in severity and extent from mild or minimal involvements of the respiratory passages to prostrating illnesses with or without pulmonary infiltration The group encompasses certain well known specific infections—i e influenza A influenza B beta hemolytic streptococcal infections and the bacterial pneumonias which are considered in other sections of this book But the greater part of the spectrum in terms of frequency of occurrence of cases is comprised of the large group of illnesses variously called the common cold coryza head cold nasopharyngitis laryngitis catarrhal fever flu grippe tracheitis bronchitis primary atypical pneumonia virus pneumonia etc The term *common respiratory disease* is employed in this section to refer collectively to this large and heterogeneous segment of the acute respiratory infections

The common respiratory diseases have not been satisfactorily classified A great deal of time and effort has been devoted to investigations of these infections but relatively little is yet known about their relationships and causation Clinical classification presents a difficult problem both in distinguishing illnesses of this group from those due to know viruses or bacteria and in separating the possible entities within the group

A group of viruses inhabiting the respiratory tract has been isolated in tissue cultures There has been confusion concerning terminology but a committee composed of interested investigators has now agreed upon the designation *adenoviruses* which will be employed hereafter Studies of the common respiratory diseases employing the adenoviruses have shed new light on the etiology epidemiology and clinical features of common respiratory disease However the results of investigations with the adenoviruses have not clarified the problem to the extent that common respiratory diseases can be discussed primarily from the etiologic point of view In civilian populations more than 90 per cent of respiratory illnesses are still of unknown or uncertain (though presumably viral) etiology

In this chapter emphasis is placed upon the general aspects of the problem but those illnesses or groups of illnesses which now appear to represent definite clinical entities are described It should be emphasized however that such segregation is mainly for convenience in describing the disease picture that the segments overlap one another and that many patients with common respiratory disease present manifestations which cannot be assigned clearly to any of the groups

History

Common respiratory disease has afflicted mankind for centuries Hippocrates (about 450 B C) and Galen and Celsus in the early Christian era described illnesses which almost certainly were respiratory infections possibly the common cold Since then many epidemics of respiratory disease have been described including influenza and others Difficulty of recognition of the various entities precludes specific interpretations in the history of common respiratory disease

Occurrence

The common respiratory diseases are world wide in distribution and no geographic area is known to be consistently free of them Certain isolated communities have been without respiratory illness for variable lengths of time but the resumption of intercourse with the outside world usually is followed by its reappearance Racial immunity or predisposition has not been established It is commonly believed that respiratory diseases are less prevalent in the warmer areas of the earth but there are insufficient data to determine whether the presumed difference is due to an actual decrease in attack rate to the occurrence of less severe illnesses to less crowding in the tropics or to incomplete observation

The respiratory diseases are highly prevalent in this country and are the most common cause of acute illness Data from industry show that they are among the leading causes of absenteeism from work Most persons have at least two or three acute respiratory infections each year

Epidemiology

The common respiratory diseases are distinctly seasonal and are confined largely to the cold months

outbreaks of human disease which appear attributable to inhalation of infected dust from barns and pens (Lennette and Welsh 1951) The method of spread of outbreaks of Q fever was not clearly established among stockyard workers in Texas and Illinois wool processers in Pennsylvania employees in a rendering plant in New York and laundry workers in Montana who hauled dirty linen from a laboratory engaged in studies in Q fever however the air borne route for dried contaminated material seems the most likely A number of epidemics have occurred among laboratory workers engaged in studies on *R burnetii* in various institutions throughout the world The disease is not transmitted from man to man

Clinical Manifestations After incubation of approximately 19 days (the range is 14 to 26) the *disease begins with headache chilly sensations* fever malaise myalgia and anorexia For several days the temperature ranges from 101 to 104 F the entire course may not exceed 2 weeks and usually ranges from 3 to 6 days There may be wide fluctuations of the fever Respiratory and gastrointestinal symptoms are not conspicuous in the early stages Headache and fever predominate A dry cough and chest pain occur after about 5 days when rales are usually audible Roentgenographic findings indistinguishable from those of primary atypical pneumonia are present usually by the third to fourth day of disease first as patchy areas of consolidation involving a portion of one lobe giving a homogeneous ground glass appearance These manifestations persist beyond the febrile period and may appear in patients who are unaware of pulmonary involvement Complications are rare and coincident with defervescence the appetite begins to return and convalescence progresses slowly for several weeks during which time the principal disability is weakness It is not uncommon for patients to lose 15 to 20 lb during the active stages of disease Several investigators have emphasized that the disease may be protracted in approximately 20 per cent of cases with fever persisting for longer than 4 weeks particularly in elderly patients Occasionally relapse occurs particularly in patients treated with antibiotics during the first several days of *disease Moreover hepatitis with the development* of clinically detectable icterus occurs in ap*proximately one third of patients* with the protracted form

Prognosis The prognosis from point of view of mortality is excellent and very few fatalities have been recorded in the modern literature Except for the patient with the protracted type of illness and hepatic involvement the course of disease is generally uncomplicated and benign

Treatment and Control Chlortetracycline oxytetracycline and chloramphenicol are effective in the treatment of patients with Q fever although the tetracycline antibiotics have been used more extensively Most patients when treated early in the course of disease respond promptly and recover without relapses The therapeutic procedures are comparable to those used in spotted fever which are discussed in detail on p 1028 It should *be emphasized that patients with hepatic involve*ment should receive careful attention to their dietary requirement particularly with relation to protein and carbohydrate intake Oxygen is beneficial in patients with severe interstitial pneumonitis

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Etiology

Present Status of the Adenoviruses These agents have been variously called the AD APC or RI group of viruses but as noted in the introduction are now known as the adenoviruses The group is large but its members can be categorized on the basis of type specificity

The adenoviruses share certain common properties They have been propagated only in tissue cultures Overt disease in common laboratory animals has not been demonstrable All strains share a common complement fixing antigen At least 17 types can be distinguished by specific antibody neutralization Thus human infection by these viruses can be recognized serologically employing acute and convalescent phase serums Though less reliable for diagnosis than serologic methods isolation of the agents from respiratory secretions can be carried out The adenoviruses appear at present to be capable of producing at least two of the four types of common respiratory disease

Present data are insufficient to allow assignment of serotypes of the virus to particular clinical syndromes Available information clearly indicates that the adenoviruses are the cause of a variable and often large proportion of cases during epidemics of acute respiratory disease of army recruits especially types 4 and 7 and occasionally type 3 Some of these recruits with acute respiratory disease have had pulmonary infiltrates Type 3 virus has been found associated with respiratory disease in civilians especially with nonbacterial pharyngitis or "pharyngoconjunctival fever" Types 1 and 2 are present in civilian populations especially in the younger age groups but have not often been associated with clinical disease

COMMON COLD

Definition The common cold is an acute infection of the upper respiratory tract in which coryza is the prominent feature Constitutional symptoms are characteristically mild and there is little or no fever The acute symptoms usually last for only a few days

Etiology Transmission of the common cold to human volunteers and to chimpanzees using bacteria free filtrates of respiratory tract secretions indicates that the disease is caused by a virus The virus has not been isolated and characterized with certainty Adenoviruses with rare exceptions are absent from the respiratory secretions of patients with the common cold and antibodies to the known types of adenovirus do not increase in titer in convalescent phase serums of patients with naturally occurring colds or volunteers with induced colds

Manifestations The onset is gradual with a sensation variously described as irritation dryness rawness or tickling in the nasopharynx or the nose Frequently chilliness or malaise accompanies the local discomfort During the next 24 to 48 hr symptoms progress to those of the "full blown" cold (Fig 145) There are coryza sneezing nasal obstruction thin nasal discharge which may be profuse a feeling of tightness in the nose mouth breathing and watery eyes Malaise lassitude chilliness headache and the subjective feeling of feverishness with little or no change in body temperature add to general discomfort and irritability Patients may be described as not feeling well enough to work efficiently but not sufficiently ill to submit to bed rest During the next 2 or 3 days systemic symptoms gradually subside the nasal discharge becomes mucoid or purulent the coryza and nasal irritation become less troublesome and nasal obstruction lessens Thick discharge and some degree of nasal obstruction may persist for several days or even for weeks the frequency with which complicating paranasal sinusitis contributes to this picture is not certain

On physical examination the nasal mucosa is reddened and edematous and nasal discharge is usually obvious The nares may be reddened or excoriated and slight tenderness over the maxillary and frontal sinuses is frequent

No two individuals describe their colds in the same way The order in which the symptoms appear is variable the pharynx may be involved and the patient may develop a troublesome irritative cough finally productive of mucoid sputum

Laboratory Findings The leukocyte count differential leukocyte count and erythrocyte sedimentation rate are normal Cultures of the nasal secretion, nasopharynx or oropharynx usually reveal only the bacteria which are common inhabitants of these areas The urine is normal

Differential Diagnosis During the first 24 or 48 hr of illness it may be difficult to distinguish the common cold from the prodromal symptoms of the acute exanthems particularly measles Coryzal symptoms or signs in a young person should always lead to a search for Koplik spots and to inquiry about possible exposure

In the early stages of meningococcal infection the only symptoms may be coryza A purpuric rash headache or signs of meningeal irritation should be investigated in all patients with coryza particularly in young individuals

The most frequent problem is the separation of the common cold from other common respiratory infections especially the milder forms of acute undifferentiated respiratory disease

The sudden onset of sneezing itching in the nose and lacrimation characteristic pale boggy appearance of the turbinates and a history of

Table 96 TRANSMISSION OF COMMON RESPIRATORY DISEASE TO HUMAN VOLUNTEERS WITH BACTERIA FREE FILTRATES OF RESPIRATORY TRACT SECRETIONS

Donor of respiratory tract secretions clinical diagnosis	Results of inoculation in human volunteers	
	Incubation period	Character of illness produced in volunteers
Common cold	18–48 hr	Symptoms predominantly coryzal constitutional symptoms minor
Acute undifferentiated respiratory disease	4–7 days	Prominent symptoms pharyngeal constitutional symptoms present illnesses mild
Primary atypical pneumonia	12–14 days	Respiratory and constitutional symptoms pulmonary infiltration

of the year in the Temperate Zones Waves of increased prevalence occur in the fall winter and spring There is however a residue of these infections throughout the year in the population The thesis has been advanced that the minor illnesses tend to predominate in the fall or early winter and severe illnesses tend to be concentrated in the late winter and spring

Since recognition of the common respiratory diseases is dependent mainly upon clinical features epidemiologic concepts are applicable only to the problem as a whole Detailed epidemiologic data and the investigation of carriers or unapparent cases must await more definite information concerning the causation and interrelationships of the various illnesses Nevertheless certain concepts have become established and may be summarized as follows

1 The air borne route of transmission appears to be the most important but not necessarily the only mode of transfer

2 Certain studies particularly those of isolated communities suggest that carriers or very mild cases are capable of transmitting respiratory infections

3 Highest attack rates occur in children under the age of five years Infants under the age of one year have relatively low rates The lowest attack rates occur in the second decade of life The curve rises slowly to a small peak in the ages from twenty five to thirty five years and then gradually declines

4 In segregated populations such as military recruits or boarding school children a wave of respiratory infections may sweep through the population shortly after the individuals are brought together These outbreaks are followed by mass insusceptibility which can last for several months or possibly much longer In the military services *this phenomenon is* considered part of the "seasoning process The explanation for seasoning is unknown but aging and immunologic phenomena are probably important factors

5 Certain studies indicate that rigorous life or exposure to inclement weather *per se* are not important factors in provoking the occurrence of the common respiratory diseases

6 An increased prevalence of the common respiratory diseases contributes in some obscure manner to the increased occurrence of the bacterial pneumonias

CLASSIFICATION

Clinical classification of the common respiratory diseases presents a difficult problem because (1) the clinical picture in individual cases often does not differ from that of several specific diseases and (2) when studied in the mass the illnesses present smooth gradations in severity rather than sharp differences and there is a vast array of symptoms and physical signs which has not yet been reduced to relative simplicity An important reason for this difficulty of clinical classification is the limited manner in which the respiratory tract can respond to infection Influenza A is a good example because the diagnosis can be confirmed by laboratory methods When a population is studied during an *epidemic it is found that cases of influenza vary* greatly in severity and that many of the cases of proved influenza do not differ clinically from other respiratory infections occurring during the epidemic and demonstrated by laboratory methods not to be influenza

The most useful clinical classification employs as criteria the site of localization of the prominent symptoms or physical signs severity of illness the presence of exudate in the throat and the presence of pneumonia

CLASSIFICATION OF COMMON RESPIRATORY DISEASE

1 Common cold
2 Acute undifferentiated respiratory disease
3 Nonbacterial pharyngitis or tonsillitis
4 Primary atypical pneumonia

Limited support for the division into these clinical groups is given by etiologic studies carried out in human volunteers Transmission experiments employing bacteria free filtrates of respiratory tract secretions show that there are at least three agents presumably viruses which are capable of causing respiratory illness (Table 96)

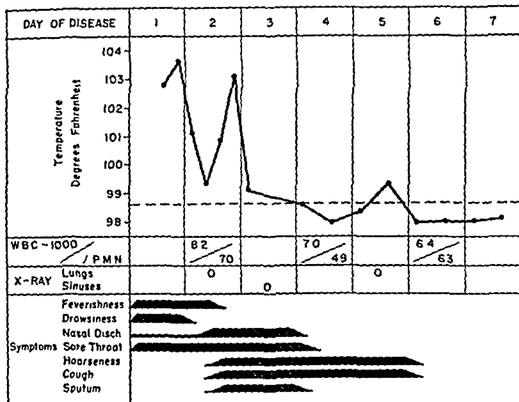


FIG. 146 Clinical chart of a patient with acute undifferentiated respiratory disease (*Commission on Acute Respiratory Diseases Fort Bragg N C J Clin Investigation* 26 959 1947)

lymphadenitis The lungs are usually clear but there may be tenderness or soreness to pressure over the sternum Pneumonitis occurs in a small proportion of cases

Acute undifferentiated respiratory disease is a more severe illness than the common cold (Fig 146) and many patients with the disease will seek or be willing to accept bed rest These patients are usually only moderately ill but occasionally may be prostrated Complete restoration of well being usually requires several days

Laboratory Findings The total and differential leukocyte counts are within normal limits although occasionally a count of 10 000 to 12,000 per cubic millimeter or even higher may be found The erythrocyte sedimentation rate is normal or only moderately increased Bacteriologic studies usually reveal only the organisms which are common residents of the respiratory tract.

In cases caused by adenoviruses the virus can be isolated from throat washings employing tissue cultures or a rise in titer of antibodies in paired acute and convalescent phase serums can be shown by complement fixation or neutralization techniques These procedures are not generally available and when employed have seldom been productive of positive results in civilian populations

Differential Diagnosis The differential diagnosis includes the common cold true influenza infectious mononucleosis primary atypical pneumonia the bacterial pneumonias and the acute exanthems in certain instances the problem becomes one of fever of unknown origin"

Influenza A and influenza B are difficult or impossible to differentiate from acute undifferentiated respiratory disease on clinical grounds although the constitutional symptoms in influenza tend to be more severe the onset may be more sudden and the conjunctivas may be injected During epidemics the diagnosis of influenza is not difficult but in the individual case the diagnosis can be made with certainty only on the basis of laboratory studies

Infectious mononucleosis should be suspected when there is enlargement of the lymph nodes in the posterior cervical triangles or elsewhere in addition to those in the anterior cervical triangles

The differentiation of *primary atypical pneumonia* from cases of acute undifferentiated respiratory disease with pneumonitis due to adenoviruses is possible only by laboratory methods

The *bacterial pneumonias* occasionally may be confused with acute undifferentiated respiratory disease during the first 12 or 24 hr of illness but the appearance of a pulmonary lesion, the more

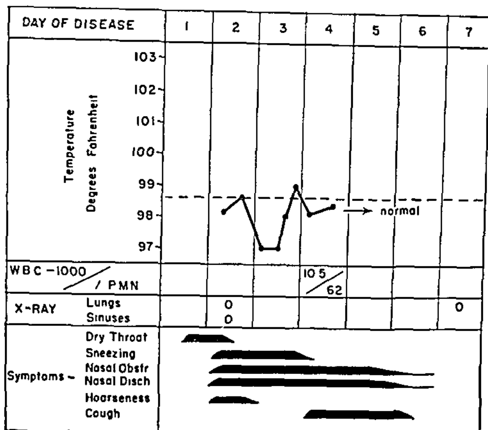


FIG 145 Clinical chart of a patient with a common cold (Commission on Acute Respiratory Diseases Fort Bragg N C J Clin Investigation 26 959 1947)

similar episodes are features which suggest allergic rhinitis rather than the common cold

ACUTE UNDIFFERENTIATED RESPIRATORY DISEASE

Definition Acute undifferentiated respiratory disease is an infection of the respiratory tract in which constitutional symptoms and fever are prominent Respiratory symptoms are likely to be localized to the throat trachea or bronchi and tend to be rather mild The illnesses in this group differ from the common cold in that they are more severe and systemic manifestations predominate over the local respiratory symptoms As employed here the term *acute undifferentiated respiratory disease* includes the *illnesses commonly called grippe or flu* but does not include influenza A or influenza B

Etiology It is not possible to delineate the etiology of acute undifferentiated respiratory disease at the present time In military recruit populations where the disease is particularly common and often occurs in epidemics the adenoviruses types 4 and 7 and to a lesser degree type 3 are the cause of many but not all such illnesses In some outbreaks only a small proportion of cases of clinically similar disease in recruits can be shown to be caused by these viruses In civilian populations several studies have revealed that type 4 and type 7 infections constitute a very small proportion of acute undifferentiated respiratory disease Thus while the discovery of the adenoviruses has not solved the over all problem of the etiology of this *group of illnesses it has clarified to some extent* the etiology of recruit illnesses

Manifestations The onset is gradual The prominent constitutional symptoms are feverishness chilliness and headache in addition malaise and anorexia are present in approximately 50 per cent of the patients The amount of fever varies widely but averages 101 F Sore throat with discomfort rather than actual pain on swallowing is the earliest and most salient respiratory symptom Hoarseness cough and discomfort in the chest described *as soreness or tightness are frequent* Nasal discharge and sneezing may occur but are usually minor The fever and malaise generally subside by the third day but *sore throat and hoarseness* often persist for a few days and it is not uncommon for the cough which may be productive of mucoid or purulent sputum to persist for one or more weeks

Physical signs are not characteristic The pharynx and fauces may be moderately reddened with prominent lymphoid follicles There is usually no pharyngeal exudate There is often mild cervical

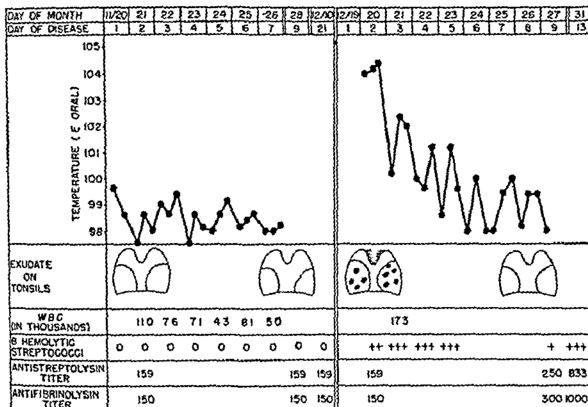


Fig 147 Clinical and laboratory data from a patient with nonstreptococcal exudative pharyngitis and tonsillitis of average severity (*left*) and from a patient with beta hemolytic streptococcal tonsillitis and pharyngitis (*right*) Note the absence of beta hemolytic streptococci in repeated throat cultures in the former and their presence in large numbers in the latter the rise in titer of antistreptolysin and antifibrinolysin (expressed in units) in convalescent phase serums in the latter the definite leukocytosis in the latter the differences in the amount of exudate on the tonsils and the presence of edema of the uvula and soft palate in the latter (*Commission on Acute Respiratory Diseases Fort Bragg N C J A M A* 133 588 1947)

infections have developed neither cold hemagglutinins nor agglutinins for streptococcus MG in their serums (2) Primary atypical pneumonia with cold hemagglutinins or streptococcus MG agglutinins or both This disease has been transmitted to human volunteers with bacteria free filtrates of sputum and throat washings and is presumed to be caused by a virus Isolation of the agent has not yet been clearly accomplished but such cases appear not to be caused by any of the known adenoviruses (3) Cases falling into neither of the above groups As yet the proportion of total cases which falls into each of these three groups is unknown Cases can be categorized only by laboratory studies

Manifestations The onset is insidious most patients have minor respiratory or constitutional symptoms for several days before consulting a physician Sudden onset is unusual

Early in the illness feverishness chilliness headache and malaise are the outstanding complaints Anorexia is common. Shaking chills are very unusual The headache is often frontal but may be occipital or generalized and is aggravated by cough the most common respiratory symptom The cough is frequently paroxysmal and harassing interfering with sleep It is nonproductive at first but mucoid or mucopurulent sputum is raised after a few days Streaks of bright red blood can appear in the sputum but grossly bloody rusty or "prune juice" sputum is very rare Substernal pain soreness or discomfort is common but pleural pain is very unusual The throat may be slightly sore dry or "scratchy"

Physical signs are not prominent especially early in the illness The patient appears mildly or moderately ill Fever rarely exceeds 104 F The pulse and respiratory rates are moderately increased Examination of the chest may reveal few signs in spite of the pulmonary lesions which are demonstrable radiographically Rales usually "sticky" in character may be heard over the involved area Early in the disease rales are audible only at the height

severe nature of the illness leukocytosis and identification of the causative agent soon clarify the picture

The disease may mimic the early symptoms and signs of the *acute exanthems* continued observation for characteristic signs of the latter disease is required

Occasionally acute undifferentiated respiratory disease may present only insignificant respiratory symptoms and brisk fever malaise anorexia and headache In such instances the appearance or intensification of respiratory symptoms may decide the issue but not infrequently the diagnosis is reached only after many other febrile disorders have been ruled out by continued observation and laboratory study Diagnosis by a process of exclusion is occasionally the only possible method

NONBACTERIAL PHARYNGITIS OR TONSILLITIS

Definition Nonbacterial pharyngitis or tonsillitis is an acute respiratory disease of unknown etiology in which exudate on the tonsils or pharynx is a distinctive feature In other respects it resembles acute undifferentiated respiratory disease rather closely but occasionally it presents symptoms and signs suggestive of beta hemolytic streptococcal tonsillitis or pharyngitis

Etiology The etiologic agent of this clinical entity is unknown in most instances The beta hemolytic streptococcus is excluded by definition Bacteriologic and limited serologic studies have indicated that other bacteria are not causative Adenovirus type 3 and occasionally other types have been found in several outbreaks of nonbacterial pharyngitis occurring principally in children in the summertime Some of these cases have had an associated conjunctivitis and Huebner and associates have employed the term *pharyngoconjunctival fever* for the condition Insufficient data are available to indicate what proportion of the total cases are caused by adenoviruses especially in adults

Manifestations Nonbacterial tonsillitis or pharyngitis is a mild disease of short duration (Fig 147 *left*) The onset is gradual as a rule The early symptoms in most cases are referable to the throat but fever or malaise is sometimes the presenting complaint The great majority of patients are febrile and develop malaise headache and anorexia During the acute illness the average maximum temperature is 101 to 102 F The febrile period is usually 2 or 3 days but may be longer

Sore throat is the most prominent respiratory symptom and is described as discomfort rawness or soreness rather than as actual pain or dysphagia Hoarseness cough and substernal discomfort are common There is a tendency for sore throat, hoarseness and especially cough to persist beyond the acute febrile period Sputum is scanty and usually mucoid

The chief physical signs are in the throat Exudate if present is white yellow or pearly gray and is located on the tonsils in the tonsillar fossae in the oropharynx or in all these areas The exudate is usually sparse and patchy The individual areas may be only pinhead in size but are frequently larger Confluent and extensive exudates are uncommon The pharynx is injected in the great majority of cases but the hyperemia is usually "streaky and only rarely is it diffuse or intense The lymphoid follicles of the pharyngeal wall are usually enlarged and reddened and frequently surmounted by small patches of exudate Edema of the soft palate or fauces is rarely prominent The lymph nodes in the anterior triangles of the neck are sometimes enlarged and tender Scattered rhonchi can be heard in about 15 per cent of cases

Laboratory Findings The total leukocyte count is usually normal but exceeds 10 000 per cubic millimeter in approximately one third of the cases The differential count is normal The erythrocyte sedimentation rate has not been adequately studied Throat cultures reveal normal flora By definition the illness is nonstreptococcal in origin and the predominance of beta hemolytic streptococci in a throat culture precludes the clinical diagnosis of nonstreptococcal exudative tonsillitis or pharyngitis

In cases caused by adenoviruses the agent has been isolated from throat washings Serologic techniques can be used to demonstrate a rise in titer of specific antibodies in paired acute and convalescent phase serums Thus far these techniques have yielded positive results more often in children than in adults but the data are not extensive

Differential Diagnosis (See p 852)

PRIMARY ATYPICAL PNEUMONIA

Definition Primary atypical pneumonia is an acute respiratory infection characterized by pulmonary lesions a paucity of physical findings in the chest constitutional symptoms cough sputum and prolonged convalescence

Etiology The etiology of primary atypical pneumonia has been a difficult problem since the condition was recognized almost two decades ago During this period several different viruses have been recovered from patients but none has been generally accepted as causally related to human disease Cases of primary atypical pneumonia can now be divided into at least three groups (1) Adenovirus infections many of which have pulmonary infiltrates and therefore are recognized as primary atypical pneumonias Patients with these

from those which occur with the common cold or acute undifferentiated respiratory disease groups

Complications of primary atypical pneumonia are unusual Pleural effusion is rare and when it occurs is almost invariably small bacteriologically sterile and readily absorbed Bacterial complications are rare Encephalitis meningoencephalitis or myocarditis occasionally occurs in severe cases and may lead to a fatal outcome Hemolytic anemia may occur during the acute illness Numerous other complications have been described but are exceedingly unusual

PATHOLOGY

The primary site of involvement in the common cold is the upper respiratory passages principally the nasal mucosa and frequently the lining membranes of the paranasal sinuses Histologically there are edema hyperemia and moderate infiltration with mononuclear cells and granulocytes Superficial necrosis and desquamation of epithelial cells ensues

The principal point of attack in acute undifferentiated respiratory disease appears to be the throat or the tracheobronchial tree rather than the nose The nature and degree of morphologic change are not known

The prominent morphologic changes in fatal cases of primary atypical pneumonia are necrotizing bronchitis and bronchiolitis and interstitial pneumonitis Multiple small endobronchial ulcerations covered with a thin grayish yellow membrane may be seen The pathologic changes are not distinctive and there are no features which distinguish them with certainty from other interstitial pneumonias Microscopic examination of the bronchi and bronchioles shows infiltration necrosis and ulceration of the walls The bronchioles are often dilated and pus epithelial cells cellular debris and mucus are present in the lumina In the pulmonary tissues surrounding the bronchi and bronchioles there are mononuclear infiltration and thickening of the alveolar septums Alveolar exudate is predominantly mononuclear Changes other than in the respiratory system are not commonly seen Acute myocarditis and hemorrhagic encephalitis have been described

PATHOGENESIS

The causative agents presumably viruses have an affinity for the mucous membrane of the respiratory tract Principal localization of the symptoms and signs to the nose in the common cold group to the pharynx in the acute undifferentiated respiratory disease and nonbacterial tonsillitis or pharyngitis groups and to the lung in the primary atypical pneumonia group suggests that the viruses of each group also possess an affinity for a particular area of the respiratory tract Limited support to the latter concept is given by the results of transmission experiments in human volunteers The widespread involvement of the respiratory tract which can occur in each of the four types of illness indicates however that the inflammatory process is more than a localized one

Data from transmission experiments employing the adenoviruses in human volunteers indicate varying success in the production of objectively recognizable illness when the inoculum is given intranasally Inoculations are usually successful however when the virus is applied to the conjunctiva As a rule human transmission experiments with the other common respiratory diseases have succeeded when the inoculum is applied to the upper respiratory passages (see Table 96) In the particular experiments noted in this table type 4 adenovirus appears to have been the agent of acute undifferentiated respiratory disease The possible natural transmission of common respiratory disease by way of the conjunctiva requires investigation

There is uncertainty concerning the role of bacteria in the pathogenesis of the common respiratory diseases but the weight of evidence indicates that bacteria are not primary incitants The chief points in favor of the hypothesis that bacteria commonly act as "secondary invaders are the facts that (1) there are reports that the total bacterial population increases as the inflammatory process proceeds especially when the secretions become thick and (2) certain specific organisms are present in large numbers in the secretions It is difficult to interpret these observations The unconvincing nature of this evidence however does not justify the categorical statement that bacteria do not act as secondary invaders in the common respiratory diseases

Evidence that "allergy" or "bacterial allergy is an important factor in the pathogenesis of common respiratory disease is neither substantial nor convincing

IMMUNITY

The isolation identification and characterization of the agents of common respiratory disease must be accomplished before an attempt can be made to evaluate the role of the parasite in the immune mechanism Repeated or successive respiratory infections in an individual do not necessarily imply lack of immunity unless it can be established that a single agent is responsible Further consideration of the role of the parasite seems fruitless until more of the agents are identified

Information concerning immunity in the host is

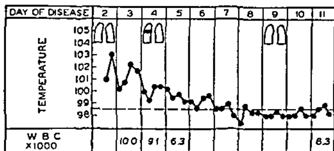


Fig 148 Clinical chart of a patient with primary atypical pneumonia of moderate severity (*Dingle et al War Medicine* 3 223 1943)

of inspiration although later in the illness rales and rhonchi are often widespread Other signs of consolidation are rarely prominent

Roentgenographic examination of the chest is the most reliable method of detecting the pulmonary lesions The pulmonary infiltrates are typically soft diffuse patchy or nodular and poorly outlined The earliest lesions often begin as a hilar enlargement which then fans out The lower lobes are most frequently involved but multilobar disease is common The lesions vary from slight stringy peribronchial shadows to extensive infiltration that is indistinguishable from that of pneumococcal pneumonia One to three weeks is usually required for resolution

The course of illness is variable In the usual case (Fig 148) fever and acute illness last 5 to 8 days Very mild illness or asymptomatic infection recognized only by roentgenograms occurs Severe illnesses are also encountered in such cases patients may be critically ill cyanotic and dyspneic

Convalescence is typically prolonged There is continued cough and return of strength and well being is slow Complete recovery without residual disability is the rule

Laboratory Findings The laboratory findings in the average case of primary atypical pneumonia are usually within normal limits *The total leukocyte count* differential formula and urine are normal Leukocytosis of 20 000 per cubic millimeter or higher can occur after the first week Early leukocytosis should suggest some other disease The erythrocyte sedimentation rate may be increased but this is not consistent Serum chloride and amino acid levels are not altered as in pneumococcal pneumonia

The appearance of cold hemagglutinins for human group O erythrocytes or of agglutinins for streptococcus MG in the blood are of value in the *retrospective diagnosis of primary atypical pneumonia* These agglutinins do not increase in titer until the second or third week after onset and are therefore not useful at the time therapeutic considerations are paramount Cold hemagglutinins are *demonstrable in approximately 50 per cent of cases* The incidence of cold hemagglutinins is increased in the more severe illnesses as judged by the height and duration of fever and the number of lobes of the lung which are involved Agglutinins for streptococcus MG are present in approximately 25 per cent of cases but the incidence increases with the *severity of illness The absence of cold hemagglutinins or agglutinins for streptococcus MG or both* does not of course exclude the diagnosis of primary atypical pneumonia

As noted above certain cases may be due to the adenoviruses particularly in military recruits and in such cases cold hemagglutinins and agglutinins for streptococcus MG have been absent

False positive Wassermann reactions occur in primary atypical pneumonia The occurrence of several other serologic reactions in convalescent phase serums indicates that serologic tests in general should be interpreted with caution in this disease

Differential Diagnosis (See p 835)

COMPLICATIONS OF COMMON *RESPIRATORY DISEASE*

Purulent paranasal sinusitis otitis media mastoiditis and bacterial pneumonia are frequent and often serious complications of the common respiratory diseases These conditions are true bacterial infections Pneumococci staphylococci and streptococci are the chief offenders Secondary bacterial infection should be suspected if fever increases or leukocytosis occurs

Several other conditions are often considered to be complications of common respiratory disease Copious thick nasal exudate postnasal discharge laryngitis hoarseness aphonia and chronic cough productive of mucoid or mucopurulent sputum occur so frequently either during the acute illness *or as the acute process begins to subside* that they may well be an integral part of the clinical picture Painful involvement of the paranasal sinuses during the acute illness seems in many instances properly to be regarded as an extension of the original inflammatory process There is much uncertainty about a role of bacteria as "secondary invaders" in these conditions

Herpes of the lips or face is particularly frequent in the common cold group However in primary atypical pneumonia herpes is so unusual that its presence strongly suggests a bacterial etiology of pneumonia

Relatively little is known about the complications in nonbacterial tonsillitis or pharyngitis There is as yet no indication that they differ appreciably

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169 INFLUENZA

Robert R Wagner

Definition Influenza is an acute respiratory infection of specific viral etiology characterized by sudden onset of headache myalgia fever and prostration The terms *influenza* and flu" should not be loosely applied to all common respiratory diseases with systemic manifestations but should be restricted to those cases with clear-cut epidemiologic or laboratory evidence of infection with influenza viruses

History Influenza is an Italian word meaning influence" (originally referring to the influence of the stars) which first came into common English usage during the European epidemic of 1743 According to the best available records the disease was uncommon in Europe during the nineteenth century until the pandemic of 1889 Subsequently the frequency and severity of epidemics increased culminating in the disastrous pandemic of 1918 which caused an estimated 20 to 40 million deaths From 1920 until the present there has been a gradual but inconstant decline in the incidence and severity of the disease The isolation of the causative organism in 1933 by Smith Andrewes and Laidlaw led to the development of simple diagnostic

still far from complete It is commonly believed that there is little or no immunity to the common cold One s personal experience of having repeated attacks of the disease often serves to confirm this conviction Furthermore experiments with human volunteers show that challenge reinoculation with common cold filtrates in the early postconvalescent period may induce a second illness Immunity to the common cold may occur but is not a solid or lasting immunity

Epidemiologic studies indicate that immunity to acute undifferentiated respiratory disease develops in army recruits following the wave of illness occurring shortly after they are brought together as a military organization How widely this principle may be applied to the acute undifferentiated respiratory disease group as a whole is an unsolved problem

Host immunity in nonbacterial tonsillitis or pharyngitis has been essentially unexplored However studies with type 3 adenovirus in volunteers have shown that type specific antibody either vaccine induced or naturally acquired affords a definite degree of protection from illness when volunteers are challenged by inoculation of the virus onto the conjunctiva

Numerous reports indicate that second attacks of primary atypical pneumonia occur even though only a few weeks or months have elapsed since the first attack Evaluation of these data is not possible because information concerning the number of agents which may cause primary atypical pneumonia is lacking

The existence of local immunity in the respiratory tract has been suggested but not proved

PREVENTION

As noted in the section on immunity studies with type 3 adenovirus vaccines have shown that a definite degree of protection against illness from challenge inoculation of the virus onto the conjunctiva is induced by the vaccine Adenovirus vaccines containing types 3 4 and 7 virus have given promising results in military recruit populations

Except for the adenovirus vaccines just noted there are no established methods procedures or immunizing agents effective for preventing common respiratory disease Various "cold vaccines" or "cold shots" are widely employed but none has as yet been shown to be of prophylactic value when tested in controlled experiments

Adequate rest a nutritious diet sensible avoidance of undue exposure to cold or wet and avoidance of exposure to those with respiratory infections seem reasonable and advisable but cannot be relied upon to prevent the common respiratory diseases

PROGNOSIS

In the absence of complications the prognosis for life is uniformly good although primary atypical pneumonia in the debilitated or in patients with chronic disease—e g cardiac disease asthma etc —may be serious or fatal Fatalities in young adults occur in approximately one in a thousand cases of primary atypical pneumonia the fatality rate in children and the aged is not established but is probably higher

TREATMENT

There is no specific treatment for common respiratory disease the sulfonamides and antibiotics at present available are not of value for the treatment of the primary illness

Symptomatic therapy is often overdone Aspirin is as good as any of the various compounds employed for the relief of feverishness headache and malaise The "antihistaminic" drugs are of little value for the treatment of the common cold or other common respiratory diseases Any of several cough sirups particularly those containing codeine are useful for the control of cough

Routine use of the sulfonamides or antibiotics for the prophylaxis of the bacterial secondary invaders is to be condemned Their use in therapeutic doses is justified when the bacterial complications are present

Patients with severe primary atypical pneumonia may be dyspneic or cyanotic the use of oxygen is very helpful and occasionally it appears to be life saving In general bed rest for a few days after the temperature is normal is advisable but resolution of the pulmonary process does not appear to be necessary before ambulation

Several reports suggest that the tetracycline drugs are of value in the treatment of primary atypical pneumonia although there is now general agreement that the sulfonamides and penicillin are ineffective Chlortetracycline appears to have been of striking benefit in many cases but in others little or no effect has been obtained It is difficult to interpret these results because the course of the disease is unpredictable Thus no definitive recommendation as to the use of the broad spectrum antibiotics in primary atypical pneumonia can be made at present

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the lumbosacral area occurs in more than half the cases this is often so severe that the patient is reluctant to move Pain and spasm localized to the abdominal muscles may simulate acute peritonitis and incapacitating periarticular pains are sometimes confused with acute arthritis Some observers have commented on the frequency of faintness and dizziness as early symptoms *Feverishness* and *chilliness* or occasionally true rigors may be the first manifestations but more often they are preceded by headache and myalgia The temperature rises abruptly to a maximum of 100 to 103 F several hours after onset rarely it may reach 106 F Thereafter the fever and pain usually subside over a 2 to 3-day period but can persist for as long as a week A common variant in the temperature course is rapid defervescence after the initial peak, with a secondary rise to the original level on the following day In general severity of illness parallels the height and duration of the fever The pulse rate is usually slow in relation to the fever but marked tachycardia can occur in severely ill patients

Prostration of some degree is almost invariable and is often the most prominent and alarming manifestation The face is usually flushed and the skin hot and dry however profuse sweating and cold mottled extremities are sometimes noted A peculiar type of "heliotrope facial cyanosis occurred during the 1918 pandemic but it is rarely seen at present Anorexia nausea and constipation are frequent secondary symptoms but vomiting and diarrhea are rare There is no evidence that influenza viruses infect the gastrointestinal tract, and the term *intestinal flu* is a misnomer Meningoencephalitis polyneuritis cranial nerve palsies transient nerve deafness aphasia hemiplegia, and other neurologic disorders have been described in association with influenza but are very unusual Hypotension heart block, and fatal myocarditis have also been reported in a few cases. The exact relationship of these neurologic and cardiovascular disorders to influenza viral infection has not been determined

Respiratory symptoms may be present at the onset but become most prominent when the systemic manifestations and fever begin to subside They are frequently less pronounced than in common respiratory disease and can be entirely absent Sneezing watery nasal discharge or stuffy nose occurs in most cases hoarseness and epistaxis are less frequent Conjunctival suffusion and burning itching watery eyes are often noted Sore throat is not a usual complaint although the throat may feel dry and the pharynx often appears slightly injected *Cough* develops during the course of the illness in more than three fourths of the cases and in about a third of these it is productive of small amounts of tenacious mucoid sputum *Chest pain* usually substernal in location and accentuated by coughing but not by breathing is present in almost half the patients Pleurisy and pleural effusion are uncommon Slight hyperpnea is often noted but the most ominous although infrequent signs are dyspnea and cyanosis which signal bronchiolar or pneumonic involvement Physical examination of the *lungs is often negative in uncomplicated influenza,* but scattered rhonchi wheezes and showers of moist rales have been reported in 5 to 40 per cent of cases in different epidemics Influenzal bronchiolitis should be suspected if rales persist in the absence of x ray evidence of pneumonitis and if the patient raises mucopurulent or blood tinged sputum

The chief *complications* of influenza are secondary bacterial infections of the paranasal sinuses middle ear bronchi and lungs The incidence of bacterial pneumonia is greatly increased during influenza epidemics even mild or asymptomatic infections with influenza viruses predispose to pneumococcal and other types of pneumonia The most serious complication in recent years has been staphylococcal pneumonia, which tends to run a fulminant often fatal course Superinfection with *Hemophilus influenzae* so common in the pandemic of 1918 is rarely encountered now

Recovery from uncomplicated influenza is often complete in 2 to 3 days or occasionally in a week but convalescence may be prolonged by "postinfectious asthenia" and depression, particularly in elderly people Minor relapses with fever can occur but are uncommon

Laboratory Findings Virus can be isolated during the acute phase of the disease by inoculation of nasopharyngeal secretions or broth garglings into the amniotic cavity of chick embryos A minimum period of 5 days is required to identify the virus Serologic diagnosis can be made by hemagglutination inhibition or complement fixation tests only if serum samples are obtained in both the acute and convalescent phases

X ray of the lungs in uncomplicated influenza is usually normal but occasionally reveals increased vascular markings basilar streaking small areas of patchy infiltration, atelectasis nodular densities or pleural effusion The blood leukocyte count can be low normal, or slightly elevated Leukocytosis above 15 000 indicates secondary bacterial infection but it is well to remember that leukopenia can occur in severe staphylococcal pneumonia Slight proteinuria is common during the febrile illness

Differential Diagnosis Many bacterial and viral infections simulate influenza at their onset, but few febrile diseases have such a self limited course The pattern of clinical manifestations becomes readily

tests which have greatly advanced knowledge of the clinical variations epidemiology and pathogenesis of the disease

Etiology There are at present three known antigenic types of influenza virus designated A B and C in the order in which they were discovered Infection with one type confers no immunity against the other two They are all approximately 100 mμ in diameter visible as spheres or filaments by electron microscopy and are biologically related by their infectivity for chick embryos capacity to agglutinate erythrocytes and affinity for the respiratory epithelium of various mammals Influenza viruses are the prototypes of the myxovirus group which also includes mumps Newcastle disease fowl plague Japanese newborn pneumonitis (Sendai) and croup viruses

Epidemiology Influenza B and C usually occur sporadically or in localized outbreaks particularly in schools and military camps Influenza A viruses are the cause of major epidemics which tend to recur in the winter months at intervals of 2 to 4 years The factors responsible for this epidemic periodicity are the decline in effective immunity of a population in interepidemic periods and the emergence every few years of new strains of virus *slightly different antigenically from the former* strains A marked change in the antigenicity of type A viruses occurred in 1946–1947 when viruses extant between 1933 and 1945 completely disappeared and were replaced by strains designated as influenza A

A further more pronounced alteration in the serotype of influenza A viruses was detected in China early in 1957 These Asian" influenza strains were widely disseminated in the Orient in the following spring and subsequently throughout the world giving rise to the Asian influenza pandemic of 1957 Certain epidemiologic and immunologic features of "Asian" influenza resemble the pandemic of 1889

Influenza A epidemics start abruptly reach a peak in 2 to 3 weeks and subside almost as rapidly The attack rate is extremely variable but at times may exceed 40 per cent of urban populations The enigma of epidemic influenza has been that outbreaks caused by the same strain of virus often appear simultaneously in widely separated areas The most likely explanation of this epidemiologic paradox is that relatively avirulent virus which causes minor or asymptomatic respiratory infections is widely seeded during the summer months It then remains dormant until external factors such as cold and inclement weather precipitate outbreaks at many foci Thereafter rapid spread of infection in susceptible individuals apparently results in increased virulence of the virus

Pathogenesis Fatal influenza uncomplicated by bacterial infection is rare at present therefore most of the information on pathogenesis comes from studies of laboratory animals *particularly ferrets* and mice After intranasal inoculation the virus multiplies to maximum levels in 24 to 48 hr and rapidly involves the entire tracheobronchial tree At first the mucosa becomes boggy and hyperemic and loses its normal ciliary activity This is shortly followed by necrosis of respiratory epithelium invasion by leukocytes pulmonary consolidation, and abnormal regeneration of metaplastic squamous epithelium The infection is confined to the respiratory tract and hilar lymph nodes of adult animals viremia is a transient and inconstant feature

Similar lesions are found in the bronchi and lungs of fatal human cases but it is not known whether they are caused by the virus itself or by secondary bacterial invaders The most frequent findings at autopsy during the 1918 pandemic were pulmonary hemorrhages necrosis of bronchial epithelium bronchiolitis squamous metaplasia of respiratory epithelium hyaline membrane formation and marked edema of alveolar walls and spaces

Manifestations The clinical features and severity of the disease vary with the age and general health of the individual Infants generally have *a benign* course with little fever whereas incapacitating or even fatal infections can occur in elderly patients particularly those with preexisting pulmonary or cardiac disease The high mortality rate in young adults that characterized the pandemic of 1918 fortunately has not recurred The disease assumes its most typical form during major epidemics of influenza A but clinical differentiation between influenza A and B is not possible in localized outbreaks Sporadic infections with either influenza A or B are likely to result in relatively minor illnesses with predominantly respiratory symptoms similar to those of common respiratory disease (see p 1042) Influenza C is particularly difficult to recognize because of its mildness Although the manifestations and severity of influenza A vary from year to year cases in a single epidemic often follow a remarkably similar pattern The clinical description that follows is a composite picture of epidemic influenza A of the past decade

The incubation period is usually 18 to 36 hr but may be as long as 3 days Mild prodromal symptoms of cough malaise and chilliness are sometimes present but extremely sudden onset is often such a characteristic feature that many patients can recall its exact time The most common initial symptom is severe generalized or frontal *headache* frequently accompanied by stabbing retroorbital pain that is accentuated by lateral or upward gaze Diffuse *myalgia* particularly marked in the legs and over

the lumbosacral area occurs in more than half the cases this is often so severe that the patient is reluctant to move Pain and spasm localized to the abdominal muscles may simulate acute peritonitis and incapacitating periarticular pains are sometimes confused with acute arthritis Some observers have commented on the frequency of faintness and dizziness as early symptoms *Feverishness* and *chilliness or occasionally true rigors may be the first* manifestations but more often they are preceded by headache and myalgia The temperature rises abruptly to a maximum of 100 to 103 F several hours after onset rarely it may reach 106 F Thereafter the fever and pain usually subside over a 2 to 3 day period but can persist for as long as a week A common variant in the temperature course is rapid defervescence after the initial peak with a secondary rise to the original level on the following day In general severity of illness parallels the height and duration of the fever The pulse rate is usually slow in relation to the fever but marked tachycardia can occur in severely ill patients

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Differential Diagnosis Many bacterial and viral infections simulate influenza at their onset, but few febrile diseases have such a self limited course The pattern of clinical manifestations becomes readily

apparent during an epidemic but many influenza outbreaks are associated with an increased incidence of other respiratory infections of viral and bacterial etiology Noninfluenzal respiratory diseases (see p 1042) are generally characterized by more gradual onset milder systemic manifestations and predominant symptoms of coryza rhinorrhea pharyngitis and conjunctivitis

Treatment Antibiotics do not affect the course of uncomplicated influenza nor is there any evidence that they prevent complications Specific chemotherapy should be reserved for secondary bacterial infections Codeine affords relief from incapacitating cough and is more effective than salicylates for symptomatic treatment of headache and myalgia salicylates often increase discomfort by causing drenching sweats and chills Bed rest and gradual return to full activity are advisable to prevent prolonged postinfectious asthenia

Prophylaxis Formalinized egg vaccines containing a mixture of influenza A and B viruses are available for subcutaneous or intradermal vaccination Although they stimulate the production of serum antibodies their value in influenza prophylaxis is limited by the following factors (1) infection can occur in spite of high levels of serum antibody (2) antibody concentration is low at the site of infection in the respiratory tract (3) vaccines are usually prepared from viruses that differ antigenically from the most recent strains and (4) even under optimal conditions their protective effect lasts only a few months Nevertheless there is ample evidence that the vaccines presently available reduce the incidence of influenza *during epidemics* in closed population groups (boarding schools and military camps) although their effectiveness in the general population is open to question The vaccines are not innocuous Fatal anaphylactic reactions have been reported in individuals sensitive to egg proteins and killed virus itself is pyrogenic and can produce an illness similar to active influenza Vaccine should never be administered to infants or young children in whom severe febrile reactions may result in convulsions and death

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170 PSITTACOSIS

Robert R Wagner and Ivan L Bennett Jr

Definition Psittacosis is an infectious disease of birds caused by a large virus Transmission of the virus from birds to man results in a febrile illness characterized by pneumonitis and systemic manifestations The name *ornithosis* is sometimes applied to infections contracted from birds other than parrots or parakeets but *psittacosis* is the more common and preferred term for all forms of the disease

History In 1880 a Swiss physician Ritter reported a fatal pneumonic illness in patients who had been in contact with sick birds Psittacosis was considered to be a rare and exotic disease until 1929 to 1930 when almost 800 cases occurred in Europe Asia and America This "pandemic" was traced to a shipment of South American parrots (Meyer 1942) Psittacosis is now a reportable disease in most states and at least 1 000 cases a year occur in the United States alone

Etiology The causative organism is an obligate intracellular parasite which is usually referred to as a virus although it more nearly resembles a rickettsia in size staining properties and susceptibility to antibiotics It is closely related to the virus of lymphogranuloma venereum and to a variety of animal viruses which have not been shown conclusively to produce human disease Psittacosis is widely distributed throughout the world and almost any avian species can harbor the virus Psittacine birds are most commonly infected but human cases have been traced to contact with pigeons ducks turkeys chickens and other birds Psittacosis can be considered an occupational disease of pet shop owners poultry raisers pigeon fanciers taxidermists and zoo attendants The incidence of human infection has steadily risen during the past decade owing in large part to the increasing popularity of parakeets and related birds as pets and the easing of regulations banning their importation and interstate shipment

Psittacosis is almost always transmitted to man by the respiratory route On rare occasions the disease may have been acquired from the bite of a pet bird The virus is present in nasal secretions excreta tissues and feathers of infected birds Although the disease can be fatal infected birds fre

quently show only minor evidences of illness such as ruffled feathers lethargy and anorexia Asymptomatic carriers are common and complete recovery can be followed by continued shedding of virus for many months Oral administration of antibiotics does not eradicate the infection in parrots and parakeets Intimate and prolonged contact is not *essential for transmission of the disease to man* a few minutes spent in an environment previously occupied by an infected bird has resulted in human infection The severity of the disease in man bears no apparent relationship to closeness or duration of contact Human to human transmission of psittacosis has occurred particularly among hospital personnel and the resulting infections are unusually severe often fatal There is evidence that these "human" strains differ slightly from native avian viruses There is no record of infection acquired by eating poultry products

Pathogenesis Psittacosis virus gains entrance to the body through the upper respiratory tract and eventually localizes in the pulmonary alveoli and the reticuloendothelial cells of the spleen and liver Invasion of the lung parenchyma probably takes place by way of the blood stream rather than by direct extension from the upper air passages A lymphocytic inflammatory response occurs on both the interstitial and respiratory surfaces of the alveoli as well as in the perivascular spaces The alveolar walls and interstitial tissues of the lung are thickened edematous necrotic and occasionally hemorrhagic Histologically the affected areas show alveolar spaces filled with fluid erythrocytes and lymphocytes The picture is not pathognomonic of psittacosis unless macrophages containing characteristic cytoplasmic inclusion bodies (L C L bodies) can be identified The respiratory epithelium of the bronchi and bronchioles is usually intact

Manifestations The clinical manifestations and course of psittacosis are extremely variable After an incubation period of 7 to 14 days the disease may start abruptly with shaking chills and high fever but the onset is more often gradual with increasing fever and malaise over a 3 to 4 day period Headache is almost always a prominent symptom it is usually diffuse and excruciating and often the patient's chief complaint Generalized myalgia is also common Spasm and stiffness of the muscles of the back and neck can lead to an erroneous diagnosis of meningitis A faint macular rash (*Horder's spots*) simulating the rose spots of typhoid fever has been described Delirium and stupor occur near the end of the first week in severe cases but other neurologic manifestations are extremely rare Occasional patients are *comatose when first seen* by a physician and the diagnosis of psittacosis may be missed in this circumstance Gastrointestinal complaints [illegible] pain nausea vomiting or diarrhea are present in some cases constipation and abdominal distention sometimes occur as late complications Icterus the result of severe hepatic involvement is a rare and ominous finding Symptoms of upper respiratory infection are not prominent although mild sore throat pharyngeal injection and cervical adenopathy are often present *Epistaxis is encountered early in the course of* nearly one fourth of the cases

The dry hacking cough of atypical pneumonia is characteristic of psittacosis it is usually nonproductive but small amounts of mucoid or bloody sputum may be raised as the disease progresses Cough may appear early in the course of the disease or as late as 5 days after the onset of fever Chest pain pleurisy with effusion or a friction rub can all occur but are not usual Pericarditis and myocarditis have been reported Most patients have a normal or slightly increased *respiratory rate* marked dyspnea with cyanosis occurs only in severe psittacosis with extensive pulmonary involvement In psittacosis as in most nonbacterial pneumonias the physical signs of pneumonitis tend to be less prominent than symptoms and x ray findings would suggest The initial examination may reveal fine sibilant rales on auscultation of the chest or clinical evidence of pneumonia may be completely lacking Rales usually become audible and more numerous as the illness progresses Signs of frank pulmonary consolidation are usually absent Patients without cough or other clinical evidence of respiratory involvement present the problem of a *fever of unknown origin* The pulse rate in psittacosis is slow in relation to the fever Splenomegaly when present in a patient with acute pneumonitis strongly suggests psittacosis Inability to feel the spleen is of no diagnostic significance however the *reported incidence* of splenomegaly has ranged from 10 to 70 per cent in different *series of proved cases* It should be remembered that the spleen is only slightly enlarged and is more frequently palpable late in the course of the disease Nontender hepatic enlargement also occurs but jaundice is rare Thrombophlebitis is not unusual during *convalescence in*deed pulmonary infarction is a common late complication and *may* be fatal

In untreated cases of psittacosis sustained or mildly remittent fever persists for 10 days to 3 weeks Defervescence is by lysis *rarely by crisis* and is accompanied by abatement of respiratory manifestations Psittacosis contracted from parrots or parakeets is more likely to be a *severe* prolonged illness than infections acquired from pigeons or barnyard fowl Relapses occur but are rare *Secondary* bacterial infections are *uncommon* Immunity to reinfection is probably *permanent*

Laboratory Findings The x ray of the lungs in psittacosis mimics a great *variety* of pulmonary dis

eases The pneumonic lesions are usually patchy in appearance but can be hazy diffuse homogeneous lobar atelectatic wedge shaped nodular or miliary The white blood cell count is normal or moderately decreased in the acute phase of the disease but may rise in convalescence The erythrocyte sedimentation rate is frequently not elevated Transient proteinuria is common The cerebrospinal fluid sometimes contains a few mononuclear cells but is otherwise normal Cold agglutinins are rarely present in the serum of patients with psittacosis

The diagnosis of psittacosis can be confirmed only by virus isolation or serologic studies The virus is present in the blood during the acute phase of the disease and in the bronchial secretions for weeks or sometimes years after infection but it is often difficult to isolate Psittacosis is most readily diagnosed by the demonstration of a rising titer of complement fixing antibody in the patient s blood An acute and convalescent specimen should always be tested Even a low titer of antibody during the acute febrile phase constitutes presumptive evidence of psittacosis The prompt initiation of treatment with tetracycline has been shown to delay antibody rise in convalescence for several weeks or months Interpretation of a single complement fixation test can sometimes be difficult because of the antigenic cross reaction between the viruses of psittacosis and lymphogranuloma venereum

Differential Diagnosis A history of exposure to birds may be the only clinical basis for differentiating psittacosis from a great variety of infectious and noninfectious febrile disorders A partial list of pneumonic diseases that can be confused with psittacosis includes primary atypical pneumonia, Q fever coccidioidomycosis tuberculosis carcinoma of the lung with bronchial obstruction and bacterial pneumonias In the early stages before pneumonitis appears psittacosis can be mistaken for influenza, typhoid fever miliary tuberculosis brucellosis infectious mononucleosis and less commonly rheumatic fever or bacterial endocarditis

Treatment The tetracyclines are consistently effective in the treatment of psittacosis Defervescence and alleviation of symptoms usually occur in 24 to 48 hr after instituting therapy with 2 to 3 Gm daily To avoid relapse treatment should probably be continued for at least 7 days after defervescence The disease will usually respond to penicillin if a daily dose of at least 2 million units is used In severe cases oxygen and other supportive measures are indicated

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Section 14 Exanthematous Viral Infections

Robert R Wagner

The exanthematous infections constitute a group of diseases caused by a variety of viruses in which the most prominent clinical feature is skin rash The nature of the rash serves as a basis for dividing these diseases into the *pox group* and the *morbilliform group* The true pox infections of man are smallpox, vaccinia and cowpox chickenpox is caused by an entirely different virus and should be considered a separate entity Present knowledge of the viral diseases characterized by morbilliform or macular eruptions suggests a classification into one subgroup comprised of measles and rubella (German measles) and another of which the prototype is exanthem subitum The latter subgroup consists of an amorphous collection of invariably mild diseases such as erythema infectiosum (Fifth disease) Boston exanthem and undoubtedly a number of as yet unclassified entities Fourth disease (Dukes disease) is sometimes included among the viral exanthems on rather sketchy evidence In addition, dengue and infectious mononucleosis are sometimes classified as exanthematous diseases but because

rash is a less consistent feature of their clinical picture they will be considered elsewhere Morbilliform rash has also been described in infections caused by ECHO viruses

The *history* of the exanthematous diseases is long and confusing At one time all epidemic eruptions (including typhus fever and scarlet fever) were considered to be variants of smallpox Measles was probably first recognized by Rhazes a tenth-century Arabian physician and its identity was finally established by Sydenham in the seventeenth century At about this time chickenpox made its appearance in medical writings but its separate status was achieved relatively recently Rubella or German measles received little recognition as a distinct entity until Koplik in 1896 firmly established the measles exanthem as a definite clinical basis for differentiating measles and rubella The first epidemics of erythema infectiosum were described under a variety of names in 1889 Exanthem subitum (roseola infantum) masqueraded as a variant of rubella and other infantile eruptions until Zahorsky s classic description in 1910 established it as a separate disease Finally Neva uncovered an outbreak of an unusual epidemic exanthem" and renamed it *Boston exanthem* in 1956 The list awaits inclusion or exclusion of a number of ill defined exanthematous diseases

The *viral etiology* of the true pox diseases has been well established for 50 years Smallpox is the human representative of a large family of mammalian viruses that are related serologically and morphologically These viruses also produce similar cellular lesions in a variety of animals Although viruses have long been suspected as the causative agents of the other exanthematous diseases failure to transmit these infections to laboratory animals other than monkeys has hampered definitive investigations Tissue culture techniques have made possible the isolation and serologic identification of the viruses of measles rubella chickenpox Boston exanthem and erythema infectiosum It should be possible in the near future to grow these agents in sufficient quantity to produce protective vaccines and diagnostic antigens

The *epidemiology* of measles rubella and chickenpox is similar They are transmitted by the respiratory route during the prodromal or pre eruptive stage Epidemics are most frequent in late winter and early spring The respiratory tract is also the commonest portal of entry of smallpox virus but in contrast to measles and chickenpox the greatest period of contagiousness is during the eruptive phase Certain epidemiologic features of exanthem subitum erythema infectiosum and Boston exanthem suggest that the respiratory tract is not the main portal of entry for these viruses The respiratory manifestations of these diseases are absent or minimal they have a relatively low degree of contagiousness and cases do not occur predominantly in the winter months In addition the viruses of Boston exanthem and erythema infectiosum have been isolated most frequently from the intestinal tract suggesting a fecal-oral route of transmission

The *pathogenesis* of the exanthematous viral diseases is not completely understood However the classical studies of Fenner on mousepox (infectious ectromelia) an endemic disease of mice that resembles smallpox serve as a model for the pathogenesis of human exanthematous diseases In mouse pox and probably in smallpox (Downie 1954) virus localizes and multiplies at the site of penetration and in adjacent lymph nodes The liver and spleen are also infected in the early stages After a definite interval of time which corresponds to the incubation period virus enters the blood stream from the lymph nodes liver and spleen and is widely distributed to the skin and mucous membranes This stage of viremia coincides with the prodromal symptoms During the next few days antibody is formed and virus disappears from the blood but continues to multiply in the skin mucous membranes and in certain instances the lung and brain This coincides with the stage of major illness characterized by skin eruption and parenchymal lesions of internal organs Measles rubella and chickenpox probably follow a similar pathogenetic pattern but differ slightly in that these viruses infect the nasopharynx only in the initial stage of disease This would account for the fact that these exanthems unlike smallpox are more contagious in the prodrome than in the major illness The pathogenesis of the benign exanthems is unknown but viremia has been demonstrated in Boston exanthem and exanthem subitum suggesting that the skin is infected by way of the blood stream

Immunity to smallpox acquired by vaccination gradually lessens over the years Immunity to the other exanthematous viral diseases is usually lifelong with a few notable exceptions In congenital or acquired defects of antibody production such as agammaglobulinemia multiple attacks of measles and chickenpox can occur It is of interest that these infections are often as mild and self limited in patients with agammaglobulinemia as in individuals who exhibit normal immune responses Chickenpox virus apparently can lie dormant in the tissues for many years flaring up in middle age to produce herpes zoster Difficulty in distinguishing the rashes of measles rubella, and other exanthems probably accounts for most reports of second attacks of these diseases Immunity to each of the exanthematous viral infections is specific and the

rarity of reinfection is evidence that a single major serologic type of virus causes each disease

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171 MEASLES (Rubeola, Morbilli)

Robert R Wagner

Definition Measles *is a highly contagious viral* disease characterized by prodromal respiratory symptoms and enanthems (Koplik spots) followed by a typical morbilliform rash

Epidemiology Measles is probably the most contagious of all diseases An isolated community in Greenland where measles was formerly unknown suffered an epidemic in 1951 in which the attack rate was virtually 100 per cent at all ages Epidemics in heavily populated areas are far less dramatic because 95 per cent of individuals above fifteen years of age have been infected previously and are immune Inapparent infections and healthy carriers probably do not occur The peak incidence is in young school children and epidemics recur at intervals of 2 to 4 years as new groups of susceptible children reach school age

Manifestations The clinical course of uncomplicated measles can be divided into three stages the *prodrome* the *eruption* and *recovery* The *prodrome* usually precedes the rash by 2 to 4 days and is characterized by symptoms of increasing fever coryza conjunctivitis photophobia hoarseness and cough The *cough* is deep seated hacking frequently *painful and may persist throughout the* entire illness The pathognomic *Koplik spots* can be found in approximately 95 per cent of cases at the end of the prodromal stage and can persist for a day or two after the onset of rash They are tiny white or bluish white areas on a bright red base characteristically grouped around the orifice of the parotid duct opposite the premolar teeth Occasionally Koplik spots cover the entire buccal mucosa they can also be present on the vaginal mucosa A prodromal rash consisting of transient blotchy *erythema may precede the true rash* The *incubation period* of measles including the prodrome is 12 to 14 days and terminates in the appearance of a *morbilliform rash* At this time fever *increases* cough worsens the face and lips become puffy and the patient appears lethargic irritable and acutely uncomfortable Headache retroorbital pain itching and burning of the eyes marked photophobia and myalgia are common Generalized lymph node enlargement can occur but is less striking than in *rubella Splenomegaly* is occasionally present The rash is first noted on the forehead and behind the ears and soon thereafter on the face and neck Classically it spreads downward in 1 to 2 days to involve the chest back abdomen and limbs including the palms and soles In the early stages the skin lesions are pink discrete macules with slightly raised irregular borders that partially blanch on pressure Later the rash becomes confluent particularly on the face and back and assumes a dusky *red or violaceous hue Rarely it is hemorrhagic* and associated with bleeding from the body orifices (black measles) The eruptive phase generally lasts for 3 to 5 days terminating abruptly with fall in temperature and marked alleviation of all symptoms *Recovery* is usually uneventful The rash fades rapidly leaving a brownish blotchy discoloration of the skin and areas of superficial desquamation

Complications Measles may be complicated by inflammation of internal organs caused by the virus *itself or by secondary bacterial infection Viral bronchitis* and *peribronchial pneumonitis* are quite common and are often mistaken for bacterial bronchitis and bronchopneumonia Viral *interstitial pneumonitis* is relatively rare this complication is characterized by diffuse nodular infiltrations of the lungs often leading to cyanosis and death Abdominal pain and diarrhea may *be manifestations* of invasion of *intestinal mucosa* and *mesenteric lymph nodes* by measles virus True viral *appendicitis* is an uncommon cause of abdominal complaints Gangrene of the face and lips or *noma* has become very rare Slight aberration of *liver function* has been observed but jaundice and hepatomegaly are uncommon Clinical and electrocardiographic evidence of *myocarditis* and *pericarditis* have been reported but their true incidence is unknown Superficial *corneal ulcerations* are often found if looked for carefully these areas usually heal without scarring but severe bacterial keratitis and blindness sometimes occur Unlike rubella there is no conclusive evidence *that measles in pregnancy is a* cause of fetal abnormalities but abortions may occur The most serious viral complication is *measles encephalitis* encountered in about one case in every 1 000 It is usually heralded by high fever drowsiness excitability and convulsions occurring at any

stage of the illness from the prodrome to a week or more after the onset of rash The mortality rate of measles encephalitis ranges from 10 to 30 per cent in different epidemics approximately 40 per cent of survivors show permanent sequelae of mental retardation personality changes and behavioral disorders

Secondary bacterial infections generally develop in the late eruptive stage and although infrequent in this decade are still the major causes of death in measles The most serious pyogenic complication of measles is *bronchopneumonia* which is associated with a high incidence of delayed resolution empyema lung abscess and bronchiectasis Purulent *otitis media* is occasionally encountered but usually does not lead to mastoiditis Rarely *bacteremia* followed by metastatic abscess formation meningitis or endocarditis may occur particularly in infants or debilitated children Paradoxically children with *nephrosis* often undergo a prolonged remission after an attack of measles Positive tuberculin reactions may revert temporarily to negative and exacerbations of latent *tuberculosis* can follow an attack of measles

Laboratory Findings Tissue culture methods for detecting measles virus and antibody are still in the experimental stage at present (1957) The simplest laboratory procedure is the microscopic examination of Wright s stained smears of nasal curettings or sputum for the characteristic multinucleated giant cells of measles (Warthin Finkeldey cells) These cells are most readily found during the late prodromal and early eruptive stages The white blood cell count may be low in the prodromal stage but is usually normal during the rash Leukocytosis occurs in secondary bacterial infections and occasionally in measles encephalitis The cerebrospinal fluid in measles encephalitis contains 0 to 500 cells per cubic millimeter mostly mononuclear cells and a slightly increased amount of protein

Differential Diagnosis In measles the rash cough and systemic manifestations are more pronounced than in rubella and exanthem subitum A problem of ever increasing importance is the differentiation of measles from drug eruptions particularly sensitivity reactions to penicillin

Treatment The treatment of uncomplicated measles is entirely symptomatic A quiet darkened room is much appreciated by the patient with irritability and photophobia Nonproductive debilitating cough is best suppressed by codeine Antibiotics should be administered *only* if secondary bacterial complications develop

Prophylaxis Immune serum is of greater benefit in prevention or attenuation of measles than of any other disease Convalescent serum is effective prophylactically but has the great disadvantage of frequently causing serum hepatitis Gamma globulin prepared from adult human serum always contains measles antibody produces few untoward reactions and is invariably free of serum hepatitis virus The dose of gamma globulin for prevention of measles is 0 1 ml per lb body weight given on the third to eighth day of the incubation period If attenuation is desired 0 02 ml per lb should be given during the first week or larger doses later in the incubation period Doses affording complete protection are advisable for infants or chronically ill children Modified measles usually results in permanent immunity but the aborted disease may not No benefit can be expected by passive immunization in the prodromal or eruptive stage Gamma globulin does not reduce the incidence or severity of measles encephalitis developing in partially protected children

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172 RUBELLA (German Measles)

Robert R Wagner

Definition This is a benign contagious disease of viral etiology characterized by fever lymphadenopathy and morbilliform rash Rubella is most important because of the high incidence of congenital malformations following maternal infection in the first half of pregnancy

Manifestations and Diagnosis The incubation period of rubella is usually 18 days with a range of 14 to 23 days A distinct prodromal period is not characteristic of the disease in children although mild fever vomiting and irritability may antedate the rash In contrast to measles rubella usually produces minimal respiratory manifestations Many patients complain of sore gums but there is little objective evidence of gingivitis An exanthem consisting of a circumscribed patch of small dark red macules resembling petechiae located at the junction of the hard and soft palates

is present in many patients (*Forchheimer spots*) but is not so constant as Koplik spots in measles In adults systemic manifestations such as chills fever to 105 F headache pain behind the eyes diffuse muscular aches and lymph node enlargement are often prominent but even severe rubella rarely causes as much discomfort or prostration as does measles The bulbar conjunctiva may be reddened but palpebral conjunctivitis and photophobia are rare The rash first appears on the neck and face as small pink macules which darken and spread downward over the trunk and extremities within 24 hr The lesions tend to remain discrete but may coalesce over the back and buttocks The palms and soles are usually not involved The rash rarely persists beyond the fourth day Fine desquamation and light brown staining of the skin sometimes occur The most characteristic manifestation of rubella is *enlargement and tenderness* of the suboccipital and postauricular lymph nodes which sometimes attain a diameter of 2 cm and are easily visible as well as palpable Mild generalized lymphadenopathy is common and splenomegaly is infrequently found

Complications are rare There is no definite predisposition to secondary bacterial infections Some patients complain of mild joint pain and swelling that may continue for several weeks after rash and fever subside *Thrombocytopenic purpura* associated with skin and mucous membrane hemorrhages has been described *Meningoencephalitis* due to the rubella virus is uncommon and not so severe as measles encephalitis It usually takes the form of a benign aseptic meningitis but fatal encephalitis can occur Peripheral neuritis and retrobulbar neuritis have also been described

The only significant *laboratory findings* are inconstant leukopenia in the preeruptive phase and lymphocytosis sometimes with abnormal lymphocytes in the stage of rash

There is no specific *treatment* and the vast majority of cases recover uneventfully Rarely relapses similar in all respects to the initial attack occur several weeks after apparent recovery

Congenital Rubella Children born to women who contract rubella in the first 4 months of pregnancy are frequently malformed Less commonly maternal rubella also results in abortion or miscarriage The principal fetal organs involved are the eye ear brain and heart singly or in combination Eye disorders consist of cataracts glaucoma and retinitis pigmentosa Malformations of the inner ear result in deaf mutism A variety of cerebral anomalies have been described including microcephaly mental retardation and possibly mongolism

Common congenital cardiac lesions are patent ductus arteriosus and interventricular septal defect The true incidence of congenital malformations following maternal rubella is unknown estimates vary from 10 to 90 per cent depending on selection of cases Physicians are frequently called upon to decide whether therapeutic abortion should be induced This question cannot be answered simply Each case should be evaluated individually after due consideration of psychologic legal and religious factors

Differential Diagnosis In addition to mild measles rubella may simulate scarlet fever and exanthem subitum Early differentiation of rubella and infectious mononucleosis is difficult at times owing to the similarity in rash adenopathy and early blood leukocyte changes

Prophylaxis Girls should be exposed to rubella before they reach the child bearing age Human gamma globulin is generally ineffective in preventing rubella unless it is prepared from rubella convalescent serum

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173 CHICKENPOX (Varicella)

Robert R Wagner

Definition Chickenpox is a highly contagious viral disease characterized by a vesicular rash The causative organism is closely related to probably identical with the virus of herpes zoster (p 1061)

Manifestations The disease occurs predominantly in school and preschool children during the late winter and early spring months It is ordinarily a mild illness in this group An *incubation period* of 14 to 16 days is regularly observed although a range of 9 to 23 days has been reported Mild prodromal symptoms such as fever malaise anorexia headache and myalgia may be present for 2 or 3 days However in most instances the initial evidence of illness is rash High fever severe myalgia prostration and occasionally delirium and stupor can occur in adults when the eruption is at its height A macular and erythematous prodromal rash occasionally precedes the true exanthem

The eruption of chickenpox be ns on the upper

trunk as small macules and papules which vesiculate almost immediately The vesicles are superficial and thin walled contain clear fluid and are surrounded by a broad zone of erythema Pruritus is often intense Slight pressure causes some of the lesions to rupture but the majority become pustular and encrusted within 48 hr Crops of vesicles continue to appear for 2 to 5 days producing the characteristic finding of lesions in different stages of development The rash is most extensive on the trunk with relatively few lesions on the face and extremities the scalp is usually involved Occasionally the lesions are extensive confluent umbilicated hemorrhagic or even gangrenous making differentiation from smallpox by inspection alone difficult The skin lesions heal rapidly without scarring unless secondarily infected with bacteria

Small superficial ulcers and vesicles on an erythematous base are frequent on the mucous membranes of the mouth and genitalia Involvement of the larynx and trachea is rare Lesions of the conjunctiva and cornea sometimes lead to scarring and impaired vision Iritis is uncommon Mild lymphadenopathy is frequent swelling of the suboccipital and posterior cervical nodes is striking when scalp involvement is extensive

Complications *Secondary bacterial infections* of the skin and scalp are common Bacterial infections of the respiratory tract usually occur in children after subsidence of fever and the acute stage of the exanthem Although fewer than 1 per cent of patients develop *bacterial pneumonia* the incidence of suppurative bronchitis is somewhat higher

Primary varicella pneumonia predominantly a disease of adults is being recognized with increasing frequency Invasion of the lungs by the virus produces an interstitial pneumonia characterized by edema and necrosis of alveolar walls hemorrhage perivasculitis and a mononuclear inflammatory response Typical intranuclear inclusion bodies have been described in macrophages and in alveolar and pleural cells Pulmonary lesions are more likely to occur in patients with extensive or hemorrhagic eruptions The onset of pneumonitis is usually abrupt with air hunger tachypnea and cyanosis developing soon after the appearance of rash Dry hacking cough is frequent and about one third of the patients produce sputum streaked with blood Chest pain occurs in half the cases and is often pleuritic Examination of the lungs is entirely negative or reveals only scattered fine rales or rhonchi The temperature is moderately elevated or normal but the pulse rate is invariably rapid Arterial hypotension or failure of the right heart may supervene X ray of the chest reveals fine miliary or nodular densities diffusely distributed throughout the lungs The duration and course of the disease are extremely variable most patients improve markedly within 72 hr but in a few patients respiratory insufficiency and roentgenographic changes persist for weeks The mortality rate in recognized cases of varicella pneumonia has been less than 15 per cent

Chickenpox *meningoencephalitis* is primarily a disease of children that resembles measles encephalitis It usually appears on about the fourth day but the time of onset varies from the first to the twenty first day Headache vomiting convulsions and stupor often occur with dramatic suddenness but the temperature rarely rises above 104 F and is frequently normal Ataxia and other signs of cerebellar disease are often conspicuous Meningismus cranial nerve palsies spastic or flaccid paralyses and hemiplegia may also be present The mortality rate is approximately 5 per cent permanent paralysis ataxia and mental retardation occur in 15 per cent of surviving cases

Other viral complications that have been described are myocarditis pericarditis orchitis and thrombocytopenic purpura Chickenpox in pregnancy may result in mild infection of the newborn infant or intrauterine death Typical herpes zoster (p 1081) occasionally occurs in individuals exposed to chickenpox and both diseases may be present simultaneously in the same patient

Laboratory Findings Fluid aspirated from the vesicles often contains multinucleated giant cells and epithelial cells with eosinophilic intranuclear inclusion bodies The lesions of herpes simplex and herpes zoster have an identical histologic appearance The blood leukocyte count in all forms of chickenpox is normal or slightly elevated unless secondary bacterial infection supervenes The cerebrospinal fluid in the encephalitic form of the disease may be normal or may contain up to 3 000 cells per cubic millimeter most of them mononuclear

Differential Diagnosis Chickenpox is readily recognizable in the vast majority of cases by the *history of exposure and the clinical picture* *Confusion* with smallpox arises particularly in adults if the eruption is widespread and hemorrhagic *Primary herpes simplex* infection of the skin (see p 1091) and *generalized vaccinia* (see p 1061) often produce recurrent crops of varicelliform lesions diagnosis of these diseases depends on a history of preexisting eczema and isolation of the specific virus *Rickettsialpox* can usually be differentiated from chickenpox by the characteristic primary eschar severe headache and specific complement fixing antibody response (see p 1031)

Treatment None of the chemotherapeutic agents is effective in chickenpox or its viral complications Local application of calamine lotion or systemic administration of antihistamines is helpful for pruritus Secondary bacterial infections of the skin and respiratory tract should be treated with appropriate

is present in many patients (*Forchheimer spots*) but is not so constant as Koplik spots in measles In adults systemic manifestations such as chills fever to 105 F headache pain behind the eyes diffuse muscular aches and lymph node enlargement are often prominent but even severe rubella *rarely causes as much discomfort or prostration as* does measles The bulbar conjunctiva may be reddened but palpebral conjunctivitis and photophobia are rare The rash first appears on the neck and face as small pink macules which darken and spread downward over the trunk and extremities within 24 hr The lesions tend to remain discrete but may coalesce over the back and buttocks The palms and soles are usually not involved The rash rarely persists beyond the fourth day Fine desquamation and light brown staining of the skin sometimes occur The most characteristic manifestation of rubella is *enlargement and tenderness* of the suboccipital and postauricular lymph nodes which sometimes attain a diameter of 2 cm and are easily visible as well as palpable Mild generalized lymphadenopathy is common and splenomegaly is infrequently found

Complications are rare There is no definite predisposition to secondary bacterial infections Some patients complain of mild joint pain and swelling that may continue for several weeks after rash and fever subside *Thrombocytopenic purpura* associated with skin and mucous membrane hemorrhages has been described *Meningoencephalitis* due to the rubella virus is uncommon and not so severe as measles encephalitis It usually takes the form of a *benign aseptic meningitis but fatal encephalitis can* occur Peripheral neuritis and retrobulbar neuritis have also been described

The only significant *laboratory findings* are inconstant leukopenia in the preeruptive phase and lymphocytosis sometimes with abnormal lymphocytes in the stage of rash

There is no specific *treatment* and the vast majority of cases recover uneventfully Rarely relapses similar in all respects to the initial attack occur several weeks after apparent recovery

Congenital Rubella Children born to women who contract rubella in the first 4 months of pregnancy are frequently malformed Less commonly maternal rubella also results in abortion or miscarriage The principal fetal organs involved are the eye ear brain and heart singly or in combination Eye disorders consist of cataracts glaucoma and retinitis pigmentosa Malformations of the inner ear result in deaf mutism A variety of cerebral anomalies have been described including microcephaly mental retardation and possibly mongolism

Common congenital cardiac lesions are patent ductus arteriosus and interventricular septal defect The true incidence of congenital malformations following maternal rubella is unknown estimates vary from 10 to 90 per cent, depending on selection of cases Physicians are frequently called upon to decide whether therapeutic abortion should be induced This question cannot be answered simply *Each case should be evaluated individually after* due consideration of psychologic legal and religious factors

Differential Diagnosis In addition to mild measles rubella may simulate scarlet fever and exanthem subitum Early differentiation of rubella and infectious mononucleosis is difficult at times owing to the similarity in rash adenopathy and early blood leukocyte changes

Prophylaxis Girls should be exposed to rubella before they reach the child bearing age Human gamma globulin is generally ineffective in preventing rubella unless it is prepared from rubella convalescent serum

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173 CHICKENPOX (Varicella)

Robert R Wagner

Definition Chickenpox is a highly contagious viral disease characterized by a vesicular rash The causative organism is closely related to probably identical with the virus of herpes zoster (p 1081)

Manifestations The disease occurs predominantly in school and preschool children during the late winter and early spring months It is ordinarily a mild illness in this group An *incubation period of 14 to 16 days is regularly observed* although a range of 9 to 23 days has been reported Mild prodromal symptoms such as fever malaise anorexia headache and myalgia may be present for 2 or 3 days However in most instances the initial evidence of illness is rash High fever severe myalgia prostration and occasionally delirium and stupor can occur in adults when the eruption is at its height A macular and erythematous prodromal rash occasionally precedes the true exanthem

The eruption of chickenpox begins on the upper

trunk as small macules and papules which vesiculate almost immediately The vesicles are superficial and thin walled contain clear fluid and are surrounded by a broad zone of erythema Pruritus is often intense Slight pressure causes some of the lesions to rupture but the majority become pustular and encrusted within 48 hr Crops of vesicles continue to appear for 2 to 5 days producing the characteristic finding of lesions in different stages of development The rash is most extensive on the trunk with relatively few lesions on the face and extremities the scalp is usually involved Occasionally *the lesions are extensive confluent* umbilicated hemorrhagic or even gangrenous making differentiation from smallpox by inspection alone difficult The skin lesions heal rapidly without scarring unless secondarily infected with bacteria

Small superficial ulcers and vesicles on an erythematous base are frequent on the mucous membranes of the mouth and genitalia Involvement of the larynx and trachea is rare Lesions of the conjunctiva and cornea sometimes lead to scarring and impaired vision Iritis is uncommon Mild lymphadenopathy is frequent swelling of the suboccipital and posterior cervical nodes is striking when scalp involvement is extensive

Complications *Secondary bacterial infections* of the skin and scalp are common Bacterial infections of the respiratory tract usually occur in children after subsidence of fever and the acute stage of the exanthem Although fewer than 1 per cent of patients develop *bacterial pneumonia* the incidence of suppurative bronchitis is somewhat higher

Primary varicella pneumonia predominantly a disease of adults is being recognized with increasing frequency Invasion of the lungs by the virus produces an interstitial pneumonia characterized by edema and necrosis of alveolar walls hemorrhage perivasculitis and a mononuclear inflammatory response Typical intranuclear inclusion bodies have been described in macrophages and in alveolar and pleural cells Pulmonary lesions are more likely to occur in patients with extensive or hemorrhagic eruptions The onset of pneumonitis is usually abrupt with air hunger tachypnea and cyanosis developing soon after the appearance of rash Dry hacking cough is frequent and about one third of the patients produce sputum streaked with blood Chest *pain occurs in half the cases and is often* pleuritic Examination of the lungs is entirely negative or reveals only scattered fine rales or rhonchi The temperature is moderately elevated or normal but the pulse rate is invariably rapid Arterial hypotension or failure of the right heart may supervene X ray of the chest reveals fine miliary or nodular densities diffusely distributed throughout the lungs The duration and course of the disease are extremely variable most patients improve markedly within 72 hr but in a few patients respiratory insufficiency and roentgenographic changes persist for weeks The mortality rate in recognized cases of varicella pneumonia has been less than 15 per cent

Chickenpox *meningoencephalitis* is primarily a disease of children that resembles measles encephalitis It usually appears on about the fourth day but the time of onset varies from the first to the twenty first day Headache vomiting convulsions and stupor often occur with dramatic suddenness but the temperature rarely rises above 104 F and is frequently normal Ataxia and other signs of cerebellar disease are often conspicuous Meningismus cranial nerve palsies spastic or flaccid paralyses and hemiplegia may also be present The mortality rate is approximately 5 per cent permanent paralysis ataxia and mental retardation occur in 15 per cent of surviving cases

Other viral complications that have been described are myocarditis pericarditis orchitis and thrombocytopenic purpura Chickenpox in pregnancy may result in mild infection of the newborn infant or intrauterine death Typical herpes zoster (p 1031) occasionally occurs in individuals exposed to chickenpox and both diseases may be present simultaneously in the same patient

Laboratory Findings Fluid aspirated from the vesicles often contains multinucleated giant cells and epithelial cells with eosinophilic intranuclear inclusion bodies The lesions of herpes simplex and herpes *zoster* have an identical histologic appearance The blood leukocyte count in all forms of chickenpox is normal or slightly elevated unless secondary bacterial infection supervenes The cerebrospinal fluid in the encephalitic form of the disease may be normal or may contain up to 3 000 cells per cubic millimeter most of them mononuclear

Differential Diagnosis Chickenpox is readily recognizable in the vast majority of cases by the history of exposure and the clinical picture Confusion with smallpox arises particularly in adults if the eruption is widespread and hemorrhagic *Primary herpes simplex* infection of the skin (see p 1091) and *generalized vaccinia* (see p 1061) often produce recurrent crops of varicelliform lesions diagnosis of these diseases depends on a history of pre existing eczema and isolation of the specific virus *Rickettsialpox* can usually be differentiated from chickenpox by the characteristic primary eschar severe headache and specific complement fixing antibody response (see p 1031)

Treatment None of the chemotherapeutic agents is effective in chickenpox or its viral complications Local application of calamine lotion or *systemic* administration of antihistamines is helpful *for pruritus* Secondary bacterial infections of the skin and respiratory tract should be treated with appropriate

antibiotics The use of cortisone or ACTH is probably warranted in the treatment of varicella pneumonia and encephalitis although adequate clinical trials have not yet been reported However fatal disseminated varicella has developed in children being treated with cortisone for other disorders

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174 SMALLPOX, VACCINIA, AND COWPOX

Robert R Wagner

The viruses of smallpox vaccinia and cowpox are closely related Each is capable of producing either local or generalized infection in man depending on the route of exposure and the state of host resistance Smallpox acquired by intradermal inoculation of virus is usually a far milder disease than naturally acquired smallpox This method of producing immunity known as variolation antedates vaccination by several centuries The classical studies of Jenner published in 1798 popularized the use of cowpox pus for active immunization against smallpox The virus used at present (vaccinia) differs slightly from cowpox virus owing either to mutation by human passage or to accidental contamination with attenuated smallpox virus Jenner s *original vaccinia virus rather than cowpox is still* used for smallpox immunization

SMALLPOX (Variola)

Definition Smallpox is a highly contagious viral disease characterized by a diphasic febrile illness and a vesicular and pustular eruption

Manifestations In its classical form (*variola major*) smallpox can be divided into a *prodromal phase* an *afebrile period* of early rash and a stage of *vesicular* and *pustular rash* The *incubation period* is usually 12 days but varies from 10 to 14 days or longer The *prodrome* starts abruptly with shaking chills fever of 104 to 106 F restlessness irritability headache excruciating backache vomiting and prostration A prodromal rash of faint irregular macules may be noted particularly in the axillary and inguinal areas An easily visible eruption at this stage usually portends a severe illness Rarely the prodromal rash is widespread and purpuric an invariably fatal form of the disease known as *black smallpox (purpura variolosa)* Mucous membrane hemorrhages bone marrow depression shock and coma accompany this fulminant illness and death occurs before the vesicular eruption develops

In most cases the initial fever subsides rapidly after 2 to 4 days and the patient seems much improved At this time a macular (followed by a papular) rash appears with individual lesions which gradually enlarge to about 0 5 cm in diameter Over a period of 6 to 10 days the papules progress to become firm multiloculated vesicles and finally painful and pruritic pustules With the appearance of pustular lesions fever and systemic manifestations recur Characteristically the rash of smallpox is concentrated on the face extremities and particularly the palms and soles However in severe infections the eruption is diffuse confluent and hemorrhagic (*variola haemorrhagica*) *Ulcerative* lesions often occur on the mucous membranes of the oropharynx conjunctivas larynx trachea and genitalia The individual lesions evolve in a regular sequence from papules to vesicles and finally to pustules and at each stage all the lesions have the same appearance The deep layers of skin are involved resulting in typical firm shotty nodules During the recovery phase the pustules become umbilicated and crusted as they heal *the deeply* situated pustules leave pitted scars In mild smallpox the lesions are sparser located in the superficial epidermis and heal without scarring they are soft friable surrounded by a red areola and may resemble closely the individual lesions of chickenpox

The *complications* of smallpox are chiefly the result of systemic reactions to the virus *Encephalitis interstitial pneumonia or myocarditis* occur rarely and are similar in many respects to infection of the brain lung or heart with measles or chickenpox virus *Superinfections with bacteria* particularly staphylococci and streptococci are seen occasionally in the late pustular stage These infections take the form of severe often fatal pyoderma or pneumonia

Benign forms of smallpox occur in certain epidemics particularly in Asia and in partially immune individuals *Alastrim (variola minor)* is characterized by low grade fever sparse rash and almost no fatalities It is caused by a virus identical to smallpox virus except for its reduced virulence

Modified smallpox (*varioloid*) is a mild form of the disease in vaccinated individuals infected with virulent virus Under these circumstances temperature elevation is minimal and the rash is less marked evolves more rapidly or may be absent A patient with smallpox modified by vaccination may transmit a fatal infection to a susceptible individual alastrim however is invariably mild

Laboratory Findings Smallpox virus can be isolated from the lesions of the skin and mucous membranes by inoculation of chick embryos mice or rabbits The virus is also present in the blood 1 to 6 days after onset Serum antibodies can often be detected as early as the fifth day of the disease by complement fixation hemagglutination inhibition and neutralization tests The leukocyte count is low in the prodromal phase leukocytosis is usual during the stage of pustular rash even in the absence of secondary bacterial infection

Differential Diagnosis Smallpox is most often confused with severe chickenpox particularly in adults In smallpox the lesions are situated in the deep layers of the skin are homogeneous and are distributed centrifugally The rash of chickenpox is superficial appears in successive crops and is located mainly on the trunk Pustular drug eruptions and erythema multiforme bullosum occasionally mimic smallpox

Treatment No specific treatment is available for the primary viral infection Although success has been reported in prevention of secondary bacterial infections with antibiotics others state that antibacterial therapy has not greatly reduced mortality Vaccination during the incubation period may result in sufficient immunity to attenuate the disease but does not prevent it All individuals in contact with a suspected case of smallpox should be vaccinated forthwith regardless of previous immunization Stringent isolation precautions until the last skin crust has separated are essential in preventing epidemic spread of the disease

VACCINIA

Definition Vaccinia is a skin infection occurring in the course of vaccination against smallpox with living vaccinia virus Generalized vaccinia and postvaccinal encephalitis are rare complications of intentional or accidental vaccination

Vaccination Vaccine is prepared by dermal inoculation of vaccinia virus into calves The processed fluid from the resulting pocks (vaccine lymph) is dispensed in sealed capillary tubes and can be kept at refrigerator temperature for several months without deterioration There are reports that lyophilized vaccines prepared from fertile eggs are effective for years after storage without refrigeration Vaccination is usually performed in the United States by the multiple pressure method When this is properly done the inoculation site is bloodless and confined to an area 1 to 2 mm in diameter Ideally vaccination should be carried out initially at four to six months of age and should be repeated on entering school and at 5 to 10 year intervals thereafter or at any time that exposure to smallpox is suspected

Three types of reaction to vaccination are distinguishable depending on the degree of host susceptibility A *primary reaction* or *take* occurs in previously unvaccinated individuals or when the level of immunity is low It is characterized by the appearance of an erythematous papule at the local site 3 to 5 days after inoculation The papule enlarges into a multiloculated vesicle which pustulates on about the ninth day Constitutional symptoms of fever malaise and irritability as well as local pain and itching are common at this time particularly in children The pustule hardens and dries and a crust is formed which usually separates at the end of the third week leaving a rough pitted scar

Partially immune individuals exhibit an *accelerated* (*vaccinoid*) *reaction* consisting of a less prominent and more rapidly evolving lesion An *immune reaction* reaches its peak in 2 or 3 days and never progresses beyond the stage of erythema and papule Failure to develop any lesion at all after vaccination is *not* an indication of immunity and calls for revaccination with a fresh batch of vaccine

Complications A variety of untoward reactions can occur following vaccination Groups of *satellite lesions* may surround the original inoculation site usually as a result of scratching or careless application of vaccine Accidental *autovaccination* of distant areas may occur from an early primary lesion a particular hazard being conjunctival infection Vaccination sites can undergo secondary bacterial infection Tetanus and syphilis were at one time hazards of vaccination but are now almost completely unknown A *false positive serologic test for syphilis* which may persist for several months sometimes follows vaccination

It is likely that vaccinia virus enters the blood stream after any primary "take" However it is only under unusual circumstances that this results in generalized infection A transient morbilliform rash (*roseola vaccinatum*) is occasionally seen 1 to 2 weeks after vaccination this probably represents abortive disseminated vaccinia Urticarial rashes which may appear at this time have been attributed to allergy to beef protein in the vaccine A more serious although uncommon complication is generalized vaccinia or Kaposi s varicelliform eruption This disorder has been described for the most part in infants and young children but in rare instances

has been seen in adults Unfortunate confusion has arisen from the application of this eponym to the disseminated dermal infections produced by herpes simplex virus in children (see p 1091) The skin lesions of generalized vaccinia are thin walled hemorrhagic bullae that are superficial and heal without scarring The disease is associated with fever prostration and high mortality More than 90 per cent of cases of generalized vaccinia have occurred in children with preexisting skin diseases such as eczema or impetigo The virus is often transmitted accidentally from a recently vaccinated sibling Therefore children with chronic skin disease should be guarded from contact with vaccinia virus An exceedingly rare but often fatal complication of vaccination is chronic *gangrenous vaccinia (vaccinia gangrenosa)* which occurs in children with impaired mechanisms of antibody formation such as agammaglobulinemia In this disorder viremia persists for months causing periodic necrotizing skin lesions Vaccination during pregnancy sometimes results in *congenital vaccinia* and is possibly associated with an increase in abortions

The exact incidence of *postvaccinal encephalitis* is unknown but is variously estimated at one case in 5 000 to 100 000 vaccinations The mean incubation period is 10 to 12 days with a range of 1 to 28 days The disease starts abruptly with high fever headache vomiting and confusion The neurologic manifestations of postvaccinal encephalitis may be limited to transient dizziness irritability and ataxia but disorientation aphasia delirium convulsions stupor and coma are seen in severe cases Nuchal rigidity is common and the cerebrospinal fluid usually shows a moderate increase in mononuclear cells and protein The mortality rate is about 40 per cent but patients who recover are usually free of sequelae Because the characteristic pathologic process is demyelinization the sobriquet of allergic encephalitis has been applied to this disease This complication is rare in infants making it advisable to vaccinate all children before the age of one year

Treatment No treatment is available for the viral complications of vaccinia other than the use of human gamma globulin in chronic gangrenous vaccinia Secondary bacterial infections should be treated with appropriate antibiotics Loose dry dressings covering the vaccination site will reduce the number of suppurative complications more effectively than impregnated occlusive bandages

COWPOX

Cowpox is an endemic disease of cattle which is transmitted to man by contact with infected cows Human disease is characterized by the appearance of single or multiple papules on the hand or other exposed skin areas These gradually enlarge into firm nodules which evolve into deep seated vesicles and pustules Inflammation and brawny edema in the surrounding tissues are frequent and painful Lymphangitis and enlargement of the lymph nodes draining the infected area are also common The disease is sometimes accompanied by fever and a generalized vesicular rash which heals without scarring The local lesion is likely to ulcerate and drain purulent material for a month or longer Serious complications such as encephalitis are exceedingly rare

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175 OTHER EXANTHEMATOUS VIRAL DISEASES

Robert R Wagner

Exanthem Subitum (Roseola Infantum)

Exanthem subitum is a sporadic infectious disease of infants and children characterized by a typical sequence of fever defervescence and rash The vast majority of cases occurs between six and eighteen months of age and the disease is rare above the age of eight although a few instances of typical roseola have been reported in young adults Exanthem subitum seldom attacks more than one child in a family and almost never reaches epidemic proportions

The *incubation period* is about 10 days but may be longer Onset is abrupt with high fever frequently reaching 105 to 106 F in a few hours Convulsions are common with hyperpyrexia but in other respects the patient appears surprisingly well There are usually no respirato manifestations

other than slight pharyngeal injection The lymph nodes are somewhat enlarged particularly in the suboccipital and posterior cervical areas Many a physician's reputation has been established by making a correct diagnosis in the preeruptive phase Constant or remittent fever persists for 3 to 5 days and then subsides completely The rash appears suddenly (hence the name *exanthem subitum*) at the time the fever disappears or as much as 36 hr later It consists of small scattered rose pink macules that blanch on pressure The *eruption* is largely confined to the neck and trunk but can involve the face and arms It usually persists for 48 hr and fades rapidly without pigmentation or desquamation The prognosis for complete recovery without sequelae is excellent Secondary bacterial infections and other complications are extremely uncommon but encephalitic manifestations and postconvulsive hemiplegia have occasionally been reported

There are no specific laboratory tests available to aid in diagnosis Leukocytosis during the febrile phase is followed by leukopenia during the eruptive stage

Erythema Infectiosum (Fifth Disease)

This is an uncommonly recognized contagious disease characterized by lack of systemic manifestations and a typical macular rash The manner in which the infection is transmitted is unknown It tends to occur in localized outbreaks particularly in elementary schools with sporadic secondary cases in family groups It has been observed at ages from eight months to forty five years but most cases are found in children from six to ten years old The *incubation period* varies from 4 to 14 days No definite prodrome occurs and the temperature is usually normal or at most transiently elevated to 100 to 102 F Respiratory and gastrointestinal symptoms are conspicuous by their absence A few patients may show slight conjunctival injection pharyngeal erythema or herpes labialis There is no enanthem or lymphadenopathy The disease is readily recognized by the rash which is the only constant manifestation It begins on the cheeks as brilliant rose red spots with well defined raised margins that rapidly become confluent The bridge of the nose is invariably spared sparse discrete lesions extend from the cheeks to the forehead and neck The rash spreads downward in 2 or 3 days to involve the extremities and to a much lesser extent the trunk The most characteristic lesions are seen on the extensor surfaces of the arms and legs and on the buttocks where large red macules separated by narrow rims of normal skin appear and assume a reticular pattern The spots fade from the center outward leaving a lacey network of red lines In the late stages this network may resemble cyanotic marbling (*cutis marmorata*) of the extremities The rash fades completely in 2 to 24 days without desquamation or residual pigmentation *The blood* leukocyte count is normal except for slight eosinophilia in some cases

Boston Exanthem

This is an acute contagious disease of children and their parents characterized by fever and a rubellalike rash The 29 patients observed in two epidemics have ranged in age between two months and thirty six years The *incubation period* varies from 3 to 8 days Fever and systemic manifestations are more marked in adults and the rash is more intense in children In adults the illness usually starts abruptly with shaking chills fever to 104 F headache muscle pains prostration and occasionally abdominal cramps or sore throat The usual findings in children are low grade fever irritability listlessness and anorexia but more often no prodromal symptoms are encountered A variety of lesions including vesicles small punched-out ulceration raised reddened areas or tiny yellowish plaques occur on the pharyngeal mucosa There is no significant lymph node enlargement The febrile or prodromal phase of the disease lasts about 48 hr The rash ordinarily appears during the 24 hr after fever subsides and consists of salmon pink macules about 2 mm in diameter with indistinct borders The lesions tend to remain discrete although they can coalesce and take on a blotchy appearance The eruption predominates over the face and upper chest but frequently extends to the arms buttocks and legs Occasionally the palms and soles are involved The rash subsides after 72 hr and recovery is always uneventful no complications or sequelae have been noted Boston exanthem is most commonly confused with German measles exanthem subitum and "heat rash"

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Section 15 Neurotropic Viral Infections

176 LYMPHOCYTIC CHORIOMENINGITIS

Lewis L Coriell

Definition Lymphocytic choriomeningitis is an acute rarely fatal viral disease of man characterized by inflammation of the meninges and choroid plexuses usually accompanied by signs of respiratory tract infection

History In 1925 Wallgren first described the clinical entity of benign aseptic meningitis for which no etiologic agent could be demonstrated Subsequently Armstrong and Lillie (1934) while studying St Louis encephalitis isolated from a monkey brain a virus that they called the *virus of lymphocytic choriomeningitis* This virus was shown to be enzootic in mice and subsequently Scott and Rivers showed it to be the cause of some but not all cases of human "aseptic meningitis An excellent general review is that of Farmer and Janeway (1942)

Etiology The virus is relatively small measuring 33 to 60 μ It is infectious for the mouse guinea pig and monkey and can be propagated in the chick embryo or in tissue culture

Epidemiology This disease accounts for 3 to 5 per cent of the cases of aseptic meningitis Most infections occur in adults between the ages of twenty and forty years There is no sex difference The disease occurs in all parts of the world and cases usually occur singly One epidemic has been proved due to this virus but case to case infection is extremely rare Since the virus usually is not transmitted from man to man one must look elsewhere for the reservoir of infection Several surveys of trapped wild mice indicate that up to 20 per cent harbor the virus and excrete it in their urine The virus has been detected in mice caught in a house where lymphocytic choriomeningitis had developed and it is probable that man is infected by inhalation or ingestion of dried infected mouse urine The disease is particularly common in the late fall and winter presumably because field mice enter dwellings at this time of year

Pathogenesis Laboratory accidents suggest that the portal of entry may be the conjunctiva the upper respiratory tract or the skin The virus can be recovered from the blood during the early stages of the disease or from cerebrospinal fluid during the period of meningeal signs and it has been recovered a few times from the nasopharynx and urine of human patients

Pathologic changes in fatal human cases have been similar to those in laboratory animals viz extensive round cell infiltration of the meninges and choroid plexuses as well as of the liver spleen, and lung Rarely the brain shows perivascular lymphocytic cuffing hemorrhages gliosis and degeneration of nerve cells

Manifestations Usually the onset of meningeal signs is preceded by 1 to 3 weeks of prodromal symptoms simulating grippe or influenza Fever (which may be remitting) chills sore throat, cough and bronchitis are most common Symptoms usually abate for a few days before the onset of headache vomiting stiff neck and photophobia, the illness in such cases being diphasic Meningeal signs may be slight and the patient rarely appears as acutely ill as in bacterial meningitis The course is usually short and complications are rare but sometimes symptoms recur one or more times after a period of apparent recovery Encephalomyelitis may occur with resulting diplopia mental changes and a variety of neurologic signs Erythematous and macular rashes have been reported in a number of cases and pneumonitis evidenced by clinical or x ray signs occurs in about half the cases during the meningeal phase The disease may simulate influenza with no signs referable to the central nervous system Subclinical infections are probably common as shown by the development of virus neutralizing antibodies in the absence of clinical disease

Laboratory Findings Leukopenia is common in the prodromal period but is not a reliable diagnostic aid The cerebrospinal fluid is frequently under normal or slightly increased pressure and contains 100 to 3 000 cells 95 to 100 per cent mononuclear The sugar and chlorides are usually normal and the protein level is slightly elevated although transient lowering of the sugar occurs in a few cases A positive diagnosis can be made only by isolation of the virus from blood or cerebrospinal fluid by intracerebral inoculation of mice or hamsters from a noninfected colony or by demonstration of a rise in serum complement fixing antibodies after the second week or of virus neutralizing antibodies after 6 to 8 weeks

Diagnosis The diseases that can mimic lymphocytic choriomeningitis are listed on p 1071

Treatment The only treatment is symptomatic

Prognosis Recovery is usually complete within 2 to 3 weeks after the onset of meningeal signs Residual neurologic damage may persist after the rare encephalomyelitic form

Cases of fatal progressive arachnoiditis and of fulminating interstitial pneumonia have been described

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177 EPIDEMIC VIRAL ENCEPHALITIDES

Lewis L Coriell

Definition The viral encephalitides comprise a large group of arthropod borne neurotropic viral diseases which occur in epidemic form The seasonal incidence geographic distribution insect vectors and animal reservoirs are specific for each of the diseases but their clinical manifestations are often similar

History Encephalitis lethargica (von Economo s encephalitis or sleeping sickness) was the first pandemic encephalitis to be recognized clinically Although a viral agent has never been identified adequate bacteriologic studies were negative and the clinical and pathologic findings were characteristic of viral infections The disease first appeared in Europe in 1915 in the United States in 1918 and sporadic outbreaks continued to occur throughout the world until 1926 Epidemics have not occurred in recent years although isolated cases presenting the same clinical picture have been described

All the other epidemic viral encephalitides have been recognized since 1930 coincident with development of the disciplines of virology It is probable that most of these diseases occurred sporadically in the past when laboratory procedures for their diagnosis were not available The dates of the first epidemic geographic locations and seasonal incidence are shown in Table 97 A more comprehensive historical review of each disease is included in the references at the end of this chapter

Etiology The causative organisms of epidemic encephalitis are small viruses that range in size from 15 to 40 mμ They can be grown in chick embryos or tissue culture or transmitted to experimental animals of which the Swiss albino mouse is the animal of choice The virus of St Louis encephalitis is not pathogenic for guinea pigs or rabbits as are the viruses of the equine encephalitides

Classification of encephalitis viruses is presently based on the geographic locale in which the disease was first described (e g St Louis encephalitis virus West Nile encephalitis virus) Others bear the names of animal disease (e g louping virus of sheep) and still another group is named for the mosquito (e g Anopheles A and B viruses) from which they have been isolated Many of these agents cause encephalitis in experimental animals but their role as human pathogens is obscure Of particular interest are Bwamba fever Semliki Forest Bunyamwera Hammon Reeves or California Ilheus and Anopheles A and B viruses because specific neutralizing antibodies are found in the serum of human beings living in certain areas Encephalomyocarditis virus (E M C) isolated originally from a gibbon with a fatal infection appears to be world wide in distribution and is closely related to Columbia SK Mengo and certain poliomyelitis viruses

Laboratory differentiation of the arthropod borne encephalitis viruses is based largely on complement fixation neutralization and animal protection tests Those that have been studied thus far fall into one of two groups The viruses of Eastern Western and Venezuelan equine encephalitis are related antigenically Another group includes the viruses of St Louis encephalitis Japanese B encephalitis louping ill Russian spring summer encephalitis and West Nile encephalitis as well as yellow fever and dengue

Epidemiology The available data strongly suggest that encephalitis viruses have complicated life cycles in lower mammals birds and arthropods often characterized by inapparent infection Man and the horse appear to be incidental hosts that are unimportant in perpetuating the viruses in nature The diseases are transmitted by biting insects that can harbor viruses for long periods Persistent viremia without manifestations of infection has been demonstrated in migratory water birds which may be responsible for transporting

Table 97 EPIDEMIC VIRAL ENCEPHALITIS

Disease	First epidemic	Virus isolated	Geographic location	Seasonal incidence	Prognosis: Mortality per cent	Prognosis: Sequelae per cent	Size	Vector	Suspected reservoir	Animal disease
Von Economo's (encephalitis lethargica)	1915	No	World wide	Winter Early spring	30	20	?	?	?	?
St Louis (SLE)	1933	1933	Central and western U S	Spring Early summer	5–30	10–40 infants 5 adults	20–30 mμ	Mosquitoes	Chicken mite Mosquitoes?	Unapparent infection with viremia in many vertebrates
Japanese B (? Russian autumn) (? Australian X disease) (Murray Valley)	1924	1936	Japan Java Philippines *Australia Korea* Manchuria Eastern Siberia Indo-China	Summer *Autumn*	45–80	Infrequent (3)	15–20 mμ	Mosquitoes	Horse? Chickens? ?	Horse unapparent infection with viremia in many vertebrates
Western equine (WEE)	1930	1930	Central and Western U S Canada Argentina	Summer	8–15	Rare	25–40 mμ	Mosquitoes	Chicken mite Wild bird mites	Equine animals
Eastern equine (EEE)	1933	1933	Eastern and Central U S and Canada Mexico Cuba Panama Brazil	Summer	65	60	25–40 mμ	Mosquitoes	Chicken mite ?	Equine animals Pheasants
Venezuelan (VEE)	1938	1938	Northern South America and Panama	? Summer	Low?	Rare	?	Mosquitoes (droplet)	?	Equine animals rodents and birds
Russian spring summer (RSSE) (Taiga tick)	1937	1937	Far Eastern provinces of U S S R Europe	Late spring Summer	30	20	15–25 mμ	*Ixodes persulcatus* (wood tick) *I ricinus*	Ticks	Woodland mammals and birds

Japanese B encephalitis from tropical areas where mosquito vectors survive throughout the year Birds are the commonest known hosts of North American encephalitis viruses but the long term reservoir is unknown although bird mites and hibernating mosquitoes have been suspected

Eastern equine encephalitis virus was originally isolated in Massachusetts but is also found west of the Appalachian Mountains and in Mexico Central America and Brazil *Aedes solicitans* is one of the mosquito vectors Infection of pheasants has been an economic problem in the Eastern United States but has not been associated with human disease which usually follows an epizootic in horses

Western equine and *St Louis encephalitis* viruses are found west of the Appalachian Mountains in the United States and Canada as well as in Argentina *Culex* mosquitoes which readily bite birds and mammals are the most important vectors

Japanese B encephalitis virus is found in temperate and tropical zones from Japan China Manchuria Siberia the Philippines and Java to Australia The disease occurs most often in children during the summer and autumn and is transmitted by *Culex* mosquitoes

Russian spring summer encephalitis is a disease of forest workers in the eastern Soviet and Siberian provinces who are exposed to bites of the tick *Ixodes persulcatus* Ticks transmit the virus to their offspring transovarially A milder form of encephalitis occurs in western Russia and eastern Europe where the suspected vector is *I ricinus* the same tick that transmits *louping ill* in Scotland and northern England

Pathogenesis Although man is usually infected through the bite of a blood sucking arthropod a stage of viremia seems to be fleeting and the virus quickly localizes in the central nervous system where it attacks the meninges and the gray and white matter of the brain and spinal cord The lesions produced by each virus resemble each other so closely that specific etiology can rarely be determined by microscopic study alone The meninges may be hyperemic and infiltrated with small mononuclear cells Small hemorrhages occur in the cerebrum basal ganglia midbrain pons or spinal cord Perivascular infiltration with small mononuclear leukocytes may completely fill the Virchow Robin spaces Degeneration and necrosis of neurones with neuronophagia may be marked and in Japanese B encephalitis striking destruction of the Purkinje cells of the cerebellum is observed Endarteritis and small areas of encephalomalacia may be present Focal areas of demyelinization are often prominent but are not confined to perivascular areas as in postvaccinal encephalitis Pulmonary congestion and visceral edema have been noted in fatal cases of eastern equine encephalitis

Clinical Manifestations The clinical picture of the arthropod borne viral encephalitides is extremely variable and is not sufficiently distinctive for each disease to permit an etiologic diagnosis Each virus may cause a variety of clinical manifestations such as (1) meningoencephalomyelitis of severe or mild degree (2) systemic illness (3) abortive infection and (4) clinically unapparent infection Greater mortality and residual damage have been observed in infants and children than in adults suggesting that age factors are more important in determining severity of infection than the specific infecting virus In general the clinical picture is that of an acute infectious disease leading to death or recovery within 2 or 3 weeks Chills may occur at the onset of Japanese B encephalitis and the erythrocyte sedimentation rate is usually elevated Postencephalitic sequelae slowly improve or remain fixed in contrast to the chronic progression typical of the sequelae of encephalitis lethargica

Most cases of encephalitis lethargica occurred in winter or early spring in people between the ages of puberty and forty five years and both sexes were affected equally The clinical manifestations were usually those of an acute febrile illness with predominant central nervous system manifestations Many patients showed progression of neurologic disease for many months The over all mortality was 30 to 40 per cent being higher in the very young and in the aged Fever was absent in some cases diagnosis becoming evident with the gradual development of parkinsonism athetosis salivation and mental changes Two syndromes were seen most frequently first *the somnolent-ophthalmoplegic* type with paralysis of the extraocular and other muscles innervated by cranial nerves oculogyric crises failure of ocular convergence apathy lethargy stupor or coma which persisted for days weeks or months and second the *irritative complex* characterized by hyperkinetic reflexes irritability and exaggerated choreiform or myoclonic movements The most frequent sequelae were "pseudopsychoneurosis" (i e headache irritability insomnia dizziness fatigue and loss of mental power) muscle weakness salivation athetosis spasticity paralysis and parkinsonism

The spinal fluid pressure was usually normal or slightly increased with a slight mononuclear pleocytosis The brain at autopsy was usually grossly normal or slightly edematous and hyperemic with minute hemorrhages in the basal ganglions midbrain and pons Histologic sections showed perivascular mononuclear infiltration neuronophagia focal encephalomalacia and demyelinization It is of interest that present knowledge of the functional relationships of the basal ganglions sprang from studies of postencephalitic parkinsonism

Laboratory Findings The total blood leukocyte count is usually between 10 000 and 20 000 per cubic millimeter with a slight increase in poly morphonuclear leukocytes However in eastern equine encephalitis total counts up to 66 000 with 90 per cent polymorphonuclears have been re corded The spinal fluid pressure is usually moder ately elevated Pleocytosis of 10 to 300 cells is the rule with mononuclear cells predominating In eastern equine encephalitis the total cell count of the cerebrospinal fluid may reach 1 000 per cubic millimeter with many polymorphonuclear leukocytes

An etiologic diagnosis can be established only by isolation of the virus from brain tissue or cerebro spinal fluid or by the demonstration of a significant rise in neutralizing or complement fixing antibodies in the patient s serum during convalescence Virus has been isolated from the blood and spinal fluid in human cases of Venezuelan equine Russian spring summer and Japanese B encephalitis how ever this is not possible in a routine hospital laboratory and for reasons of expense equipment and safety should not be attempted except by trained workers Specimens for virus isolation should be collected aseptically and promptly delivered to the virus laboratory For serologic diagnosis blood should be drawn very early in the disease and a second specimen 3 weeks later The serum should be separated as soon as the clot has retracted and kept frozen until both serums can be tested together

Treatment There is no specific treatment for any of these diseases after symptoms develop None of the chemotherapeutic agents available at present is of benefit Supportive therapy control of con vulsions maintenance of adequate nutrition and good nursing care are essential Physical therapy muscle training and psychotherapy may be valua ble in the treatment of sequelae Treatment with hyperimmune and convalescent serums has not been beneficial

Prophylaxis Formalized vaccines for many of these diseases have been prepared from infected brain tissue culture or embryonated eggs and pro tective effects have been demonstrated in animals Vaccination of horses and mules has proved suc cessful in this country and woodcutters have been protected by a mouse brain vaccine in Russia Laboratory workers and others exposed to special hazards should be vaccinated

Prognosis The rates of mortality and of sequelae are shown in Table 97

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178 POLIOMYELITIS

Louis Weinstein

Definition Poliomyelitis is a common acute viral infection which occurs naturally only in man and produces a wide variety of clinical manifestations In its most severe form it involves parts of the central nervous system In most instances the nerv ous system is not invaded infection may take place without apparent illness or it may result in the pro

duction of nonspecific syndromes or in invasion of the nervous system with or without the development of dysfunction

Etiology The causative agent of poliomyelitis is a virus ranging from 8 to 30 mμ in diameter pathogenic for man monkeys and chimpanzees Three antigenically distinct types have been defined type I (Brunhilde) type II (Lansing) and type III (Leon) Although some degree of cross neutralization is demonstrable in highly immunized experimental animals infection in man with one type does not protect against invasion by another Poliomyelitis virus grows well in tissue culture

The viruses of poliomyelitis may remain viable in water or sewage under proper conditions for as long as 4 months They are not killed by ether Merthiolate tincture of Zephiran ethyl alcohol or low concentrations of phenol but are inactivated by heat bichloride of mercury oxidizing agents 2 per cent tincture of iodine ultraviolet light and 10 min exposure to a chlorine concentration of 0 05 ppm

Epidemiology Poliomyelitis is world wide but epidemics have been limited to a relatively small number of areas That the disease is much more prevalent than is suggested by the number of clinically recognized cases is proved by the widespread distribution of neutralizing antibody to the virus in population groups in which it was thought to be rare In areas where infection without involvement of the nervous system occurs about 95 per cent of the disease is clinically unapparent Poliomyelitis occurs mainly in the warm months of the year with the highest frequency from July through September in the North Temperate Zone although it may appear as early as April or as late as December In tropical or subtropical regions the season" may be prolonged

Certain environmental factors are of importance in determining the risk of exposure to poliomyelitis virus and the development of infection In areas of poor sanitation most individuals develop neutralizing antibodies in early childhood whereas in localities where sanitation is good the peak of population immunity is not reached until fifteen years of age or older Urban dwellers become immune earlier than those who live in rural areas In lower income groups evidence of contact with poliomyelitis virus appears at a younger age than in individuals whose financial status is good this may only reflect differences in crowding and sanitation In some parts of the world certain racial groups appear to be more susceptible than others but this is not constant for a particular race in a different area

Poliomyelitis was most common in the preschool child until about 25 years ago In the past quarter of a century however it has been increasing in older age groups in some recent epidemics 25 to 30 per cent of patients have been older than fifteen years of age The increase in adult cases is not due merely to aging of the population or increased reporting of paralytic and nonparalytic cases Young children are still affected more often than adults Paralytic disease has been described in the neonatal period and late in the sixth decade of life but is very uncommon at these age extremes

Pathogenesis Man is the sole reservoir of poliomyelitis virus Human carriers especially those with unapparent infection are most important in transmission of the virus to susceptible contacts history of contact with recognized cases is uncommon Milk has been incriminated as the source of infection in one epidemic

Virus is present in the stool and oropharynx of patients with poliomyelitis regardless of the clinical type of disease It is recoverable from pharyngeal secretions for only a few days but is demonstrable in the feces for several weeks The weight of opinion favors the intestinal tract as the main source from which virus is disseminated The mode of infection is therefore fecal oral the same as that in salmonellosis shigellosis and other enteric infections Very small quantities of stool contain thousands of infective doses of poliomyelitis virus Large quantities of virus are present in sewage drained from areas in which the infection is present The role of the fly in the transmission of poliomyelitis is not settled Flies trapped in areas close to cases of poliomyelitis may carry the virus Food exposed to flies from homes in which poliomyelitis was present has produced the disease in monkeys to whom it was fed Attempts to reduce the spread of disease in epidemics by eradication of the fly population however has not been successful Poliomyelitis is as highly communicable as measles or varicella in individuals under fifteen years of age infection with or without clinical manifestations occurs in 100 per cent of household and 87 per cent of daily contacts

The theory that poliomyelitis virus multiplies only in nervous tissue and reaches the central nervous system only by way of peripheral nerves from the pharynx or intestinal tract has been seriously questioned because of the demonstration of viremia prior to the onset of clinical manifestations Although the exact mechanism still remains to be proved, the following sequence of events has been postulated on the basis of experimental and clinical observations (1) The virus enters by way of the mouth and begins to multiply in the oropharynx and lower intestinal tract It escapes from either area there is no conclusive evidence as to which is more important in transmission The site of viral growth is probably extraneural Virus is present in pharyngeal secretions and stool during the incubation period it has been demonstrated in the feces

as long as 19 days prior to onset of the disease (2) The phase of minor illness (described below) develops in association with the presence of the virus in the blood throat and feces the viremia persisting for only a few days until antibodies make their appearance The following migration of the infectious agent has been suggested Virus in the intestinal tract penetrates the lymphatic channels and enters the blood stream from which it is dis seminated into the interstitial tissue spaces and then reaches the lymph nodes where it may be detected for a period after the stage of viremia There is still some question whether viremia is primary and is followed by invasion of the nervous system or whether it is merely a manifestation of spill over from already infected neural tissues (3) The final *stage in the pathogenesis of poliomyelitis is invasion* of the nervous system This is thought to follow the viremic stage during which the agent gains a foothold in the nervous system in which it multi plies It has been suggested that the virus enters the nervous system from the blood at one point perhaps the area postrema in the medulla ob longata because this is more penetrable than other parts of the brain to dyes injected intravascularly it has also been postulated however that viral in vasion of the nervous system occurs at many points by direct passage of virus from capillaries to neu rones Once the infectious agent has reached the nervous system it spreads along nerve fibers

Central nervous system invasion in poliomyelitis results from the simultaneous operation of two groups of factors (1) those associated with the virus and (2) those related to the host Strains of poliomyelitis virus vary greatly in their ability to invade nervous tissue from the blood or intestinal tract and to destroy neurones Repeated passage in animals or tissue cultures induces changes in invasive capacity without affecting the basic anti genic character of the agent One of the host fac tors important in determining susceptibility to dis ease of the nervous system is type specific neutraliz ing antibody which is present even before the onset of symptoms The early presence of detect able immunity is in favor of multiplication of virus in nonnervous tissue and accounts for the short persistence of virus in the pharynx and blood sites in which antibody is demonstrable The persistence of virus in the nervous system and intestine is probably due to the difficulty which antibody has in reaching these areas

The most important determinant of human sus ceptibility to poliomyelitis is *serum antibody* Pre vious inapparent infection and illness without in vasion of the nervous system are common in areas where the paralytic form of the disease occurs these produce resistance to reinvasion Many chil dren and most adults possess neutralizing antibody for all three types of virus this probably accounts for the relative infrequency of the disease in older age groups Infants under six months old rarely get poliomyelitis because immunity is passively transferred from the mother Babies born to women in the acute phase of poliomyelitis can develop the disease shortly after birth The sex of patients plays a role in determining susceptibility Among chil dren males are affected more often than females the opposite is true in adults *Pregnancy* increases the risk of clinically apparent poliomyelitis Multi parous females are more susceptible than primip aras The disease is somewhat more frequent in the second than in the first or third trimesters *Menstruation* or *ovulation* appears to heighten sus ceptibility *Absence of the tonsils and adenoids* re gardless of the time of their removal is associated with a marked increase in incidence of bulbar polio myelitis *Chilling or physical exertion* after in vasion by the virus leads to more frequent develop ment of paralytic poliomyelitis especially in adults

CLINICAL MANIFESTATIONS DIAGNOSIS AND COURSE

The incubation period of poliomyelitis varies from 3 to 35 days about 80 per cent of cases occur within 6 to 20 days after contact with the virus The disease may assume one of four forms (1) unapparent infection (2) minor illness (3) non paralytic poliomyelitis (4) paralytic poliomyelitis

Unapparent Infection

In families in which a clinically recognized case of poliomyelitis is present other susceptible mem bers usually develop unapparent infection The bulk of infection with the virus of poliomyelitis (95 per cent) occurs in this form There are no symptoms but the virus is present in the pharynx and intes tine It is probably also present in the blood Type specific neutralizing antibody usually develops

"Minor Illness"

The entire course of poliomyelitis may consist of a nonspecific illness without clinical or laboratory evidence of central nervous system invasion this is abortive poliomyelitis Three syndromes have been observed (1) upper respiratory manifestations consisting of fever of varying degree pharyngeal discomfort with or without coryza and reddening and swelling of the lymphoid tissues of the throat (2) gastrointestinal disturbances with nausea vom iting diarrhea or constipation and abdominal dis comfort accompanied by moderate fever (3) grippelike disease with fever and generalized aching of muscle bones and joints resembling influenza Virus can be demonstrated [illegible]

and blood in the early stages of these "minor" illnesses Type specific neutralizing and complement fixing antibodies develop during convalescence

Nonparalytic Poliomyelitis

Nonparalytic poliomyelitis consists of prodromal manifestations signs of meningeal irritation and abnormalities of the spinal fluid The prodrome is similar to that of the "minor" illnesses and is usually present for several days before the onset of other signs it may be entirely absent Stiffness of the neck and back positive Kernig s signs and with severe meningeal irritation leg and neck Brudzinski s signs are present The tripod (patient extends arms behind back with hands on bed for support when sitting up) and Hoyne s signs (head falls back when with patient in supine position shoulders are elevated) can be elicited in paralytic or nonparalytic poliomyelitis but are not pathognomonic The spinal fluid usually contains between 25 and 500 cells rarely as many as 1 000 to 2 000 Very early in the disease there is often a preponderance of neutrophils (up to 80 per cent) within a few days however mononuclear cells predominate The protein is normal or slightly elevated at the beginning of the illness but may increase to between 50 and 100 mg per 100 ml The sugar content is normal or moderately elevated These findings indicate an inflammatory reaction of the meninges but are not diagnostic of poliomyelitis They are also present in healing bacterial meningitis tuberculous meningitis focal embolic encephalomyelitis (subacute bacterial endocarditis) scarlet fever pertussis encephalopathy leptospiral meningitis syphilis mumps meningitis Coxsackie virus infections herpes simplex meningitis infectious mononucleosis *Trichinella* meningitis brain abscess multiple sclerosis tumors of the brain or spinal cord allergic reactions involving the nervous system postinfectious encephalitides "infectious" polyneuritis and lymphocytic choriomeningitis The diagnosis of nonparalytic poliomyelitis on clinical grounds alone is *impossible because the signs symptoms and* laboratory findings are completely nonspecific Viral and immunologic studies suggest that less than 40 per cent of cases of "nonparalytic poliomyelitis" are actually this disease mumps meningitis without salivary gland involvement (p 1083) and Coxsackie virus disease (p 1089) are the two most common differential diagnoses

The course of nonparalytic poliomyelitis is benign Defervescence usually occurs in 3 to 5 days but meningeal irritation may persist for as long as 2 weeks No changes in reflexes or in muscle and cranial nerve function are detectable The white blood count may be as high as 15 000 in the early stage of the disease but is usually normal within 1 week The spinal fluid often shows mononuclear pleocytosis and elevated protein for 2 to 3 weeks after the onset of the disease

Paralytic Poliomyelitis

The syndrome of paralytic poliomyelitis consists of prodromal manifestations ("minor" illness) signs of meningeal irritation abnormal spinal fluid and signs of involvement of motor nerve cells in the spinal cord brain or cranial nerve nuclei resulting in paresis or paralysis of various muscles Lesions may also be present in parts of the nervous system other than anterior horn cells the precentral gyrus the reticular formation in the medulla, the roof nuclei and vermis of the cerebellum Auerbach s and Meissner s plexuses and sympathetic ganglions are usually found to be involved in fatal cases Seldom however are there clinical signs pointing to disease of these parts "Skip" areas are common in spinal paralytic disease e g involvement of the cervical and lumbar cords is often present with no dysfunction of the thoracic portion

Paralytic poliomyelitis may be subdivided into the following types

I Spinal
- *A* Cervical
- *B* Thoracic
- *C* Lumbar
- *D* Any combination of *A* *B* and *C*

II Bulbar
- *A* Upper cranial nerve involvement—III IV V VI VII VIII
- *B* Lower cranial nerve involvement—IX,X,XI,XII
- *C* Involvement of cardiorespiratory centers

III Bulbospinal

IV Polioencephalitis—paralytic or nonparalytic
- *A* Diffuse encephalitis
- *B* Focal encephalitis
- *C* Cerebellar involvement (?)
- *D* Bulboencephalitic disease
- *E* Spinalencephalitic disease

Prodromal manifestations are often absent in paralytic poliomyelitis In some cases the illness is biphasic in character In these cases the disease starts with fever and manifestations of one of the "minor" illnesses After several days all symptoms disappear in 5 or 10 days there is recrudescence of fever the development of signs of meningeal irritation and the appearance of paralysis The commonest prodromal symptoms in adults are generalized muscle and bone discomfort In children upper respiratory tract syndromes are most frequent The spinal fluid findings in paralytic poliomyelitis are the same as those in the nonparalytic disease and bear no relationship to *the severity of* involvement or prognosis It has been stated that the spinal fluid is completely normal in about 10 per cent of cases of poliomyelitis This incidence is

too high because of the inclusion of cases of non paralytic poliomyelitis many of which as pointed out above are instances of some other disease In the writer s experience paralytic poliomyelitis may be accompanied by a completely normal spinal fluid throughout its entire course but this occurs in no more than 0 5 per cent of cases In some patients decrease in number of cells in the spinal fluid is accompanied by a progressive rise in protein which may reach levels high enough to cause confusion with the cytoalbuminologic dissociation observed in infectious polyneuritis

Spinal Paralytic Poliomyelitis In the early stages of spinal paralytic poliomyelitis cramping pain in the muscles innervated by the affected neurones and hyperesthesia of the overlying skin are present The discomfort may be very severe muscle spasm the exact mechanism of which is not clear is usually detectable Paralysis may not appear for some *time after the onset of symptoms In some instances* increase in muscle weakness is very slow in others it becomes widespread within 48 hr Rarely a rapidly ascending paralysis of the Landry type is observed Age is one factor in determining the extent of involvement In children less than five years old paresis of one leg is most common In patients between five and fifteen years of age weakness of one arm or paraplegia is most frequent while in *adults (sixteen to sixty five years old) quadriplegia* is observed most often Dysfunction of the urinary bladder is at least ten times more frequent in adults than in children Paralysis of the muscles of respiration is most common in those older than sixteen years of age Infants younger than one year are subject to very extensive involvement Among adults men develop quadriplegia respiratory paral*ysis and loss of bladder function more frequently than do women Pregnancy does not increase the* severity of the disease unless parturition takes place during the acute phase There is a definite association of inoculation of antigenic materials (triple vaccine for example) with an increased risk of involvement of the muscles around the site of injection

The location of muscle weakness depends on the portion of the spinal cord affected Isolated infection of the cervical thoracic or lumbar areas may be present or two or more parts of the cord may be involved simultaneously The lumbar area is the one most frequently damaged

When the cervical portion of the spinal cord is involved there is paresis or paralysis of *the muscles* of the shoulders arms neck and diaphragm Very early in the disease the reflexes in the arms remain lively they diminish rapidly however and are usually absent by the time paralysis has become established Coarse twitching of the affected shoulder or arm muscles is common With cervical cord disease there is always danger of respiratory paralysis due to spread of the infection to the motor nuclei of the phrenic nerves and medulla

Weakness of the muscles of the chest upper portion of the abdomen and spine follows involvement of the thoracic portion of the spinal cord Difficulty in breathing results from dysfunction of the intercostal and other thoracic muscles The chest wall may be in spasm and may appear rigid despite the presence of only a minor degree of paresis Twitching *of the thoracic abdominal or spine* supporting muscles may sometimes be noted

Disease of the lumbar portion of the spinal cord produces weakness of the muscles of the legs and inferior portions of the abdomen and back Again pain tenderness "spasm and twitching herald the oncoming paralysis and the reflexes are abolished with the development of flaccid paralysis Dysfunction of the iliopsoas muscles indicated by inability *to sit up from a lying position the hip muscles* quadriceps femoris hamstring and gastrocnemii peroneals anterior tibials ten or fasciae latae glutei and sartorious may occur in various combinations In adults complete paraplegia is not infrequent Paralysis of the urinary bladder usually temporary occurs in about one third of patients over sixteen years of age and is rarely observed in the absence of weakness of the legs

The abdominal and cremasteric reflexes usually disappear before muscle weakness is marked in paralytic poliomyelitis and may be absent during the entire course of the disease An extensor plantar response (positive Babinski) has been elicited in a few cases during the first 1 or 2 days but is a rare finding its persistence or late development is incompatible with poliomyelitis Hyperesthesia of the *skin is frequent Sensory loss does not occur Constipation abdominal cramps and meteorism* are common in spinal paralytic poliomyelitis and are due to partial ileus resulting from involvement of the autonomic nervous system and weakness of the abdominal muscles When the disease is severe sympathetic nervous system disturbances with tachycardia hypertension abnormal sweating and cyanosis and coldness of the involved extremities not due to superficial vasospasm are present

Fever in spinal paralytic poliomyelitis is usually present for the first few days of the disease and disappears by lysis In about 90 per cent of cases there is little or no extension of paralysis after defervescence has been established for about 48 *hr In about 10 per cent however progression* of weakness may continue for as long as a week or more and may be of notable degree

Bulbar Poliomyelitis The incidence of bulbar poliomyelitis differs from one epidemic to another and varies between *6 and 25 per cent In patients* subjected to tonsilloade

of onset of the disease and in those in whom the operation was carried out years before the bulbar form of infection is present in about 85 per cent of cases Pure bulbar involvement (without any signs of spinal cord involvement) is commonest in children adults with bulbar disturbances usually have associated spinal paralyses The prodromal manifestations of bulbar poliomyelitis are often the same as in the spinal form The syndromes which develop depend on the area of the brain stem involved and result from damage to the medulla pons and midbrain Signs and symptoms are produced by (1) dysfunction of the upper cranial nerve nuclei (2) damage to the lower cranial nerve nuclei and (3) disturbances of the respiratory and vasomotor regulating centers in the medulla Combined bulbar and diffuse or focal encephalitis or spinal involvement may occur

Upper Cranial Nerve Nuclei–III IV V VI VII VIII Isolated ocular nerve palsies total external ophthalmoplegia pupillary disorders and Horner s syndrome occur There may be unilateral or bilateral involvement of the fifth nerve with difficulty in chewing and closing the mouth as well as deviation of the jaws Paralysis of the seventh cranial nerve is common and usually unilateral the entire face or only the upper or lower parts may be affected Disturbances of vestibular function and deafness resulting from damage to the nucleus of the eighth nerve occur infrequently

Lower Cranial Nerve Nuclei–IX X XI XII Life may be endangered when the muscles of deglutition are paralyzed because of involvement of the nucleus ambiguus in the medulla With involvement of these nerves the voice has a nasal quality and movement of one or both halves of the soft palate is decreased or absent Saliva collects in the hypopharynx because of difficulty in swallowing and not because of excessive secretion Hoarseness and laryngeal stridor follow weakness or paralysis of the vocal cords Unilateral or bilateral weakness of the tongue sternocleidomastoid and trapezius muscles may be present Inability to swallow results in pooling of saliva and food in the pharynx with obstruction to the airway Aspiration of fluid into the larynx reflex spasm of the glottis and abductor paralysis of the vocal cords constitute very serious threats to life Minor or major pareses of the soft palate and pharyngeal muscles are detectable by a nasal quality of the voice

Disease of the medullary respiratory center produces irregularity of the rhythm depth and rate of breathing Respirations are shallow and as the disease progresses are interrupted by longer and longer periods of apnea until breathing stops completely The thoracic muscles and diaphragm are not weak unless spinal involvement is present Hiccoughing is frequent in the early phase of respiratory center dysfunction Hypoxia without visible cyanosis is common and contributes to the intensity of the manifestations In the late stages cyanosis unresponsive to oxygen administration is commonly present and the temperature pulse rate and blood pressure are elevated The final event is usually shock which in the majority of cases is irreversible despite heroic measures

The manifestations of involvement of the circulatory regulating center are a deep cherry red color of the lips flushed florid appearance of the skin a very rapid irregular pulse small pulse pressure when the blood pressure is normal and moderate to severe hypotension Hyperthermia cold mottled clammy skin shallow respiration and anxiety restlessness and confusion appear as the circulatory mechanism becomes progressively more impaired and irreversible shock develops

Polioencephalitis Encephalitic symptoms occur as isolated syndromes or together with bulbar or spinal poliomyelitis The incidence of polioencephalitis is variable one small epidemic in which most of the patients had this type of disease has been described Symptoms of diffuse or focal involvement of the brain may be present The diffuse form is characterized by confusion agitation anxiety with a feeling of impending doom or somnolence Quivering trembling twitching and jerking of the facial muscles and extremities Flushing of the face tremor of the hands and restless movements occur Insomnia may be severe In fatal cases the confusion is marked and progresses to lethargy and death

In focal polioencephalitis there may be clinical evidence of brain damage or the lesion may be silent and demonstrable only at necropsy Visual verbal agnosia myoclonic jerks grand mal convulsions which occasionally persist for a long time after recovery spastic hemiparesis ataxia of one arm or leg and hydrocephalus have been described

The diagnosis of paralytic poliomyelitis can usually be made on clinical grounds The outstanding manifestations are a lower motor neurone lesion of rapid development with flaccid weakness and hypo or areflexia Signs of upper motor neurone disease or decreased sensation are not compatible with poliomyelitis Among the diseases which may cause confusion especially in their early stages are toxic infectious or idiopathic polyneuritis the post infectious encephalitides viral encephalitides trichinosis acute rheumatic fever cerebrovascular accidents with paralysis acute syphilitic meningitis (frequent cranial nerve palsies) meningomyeloencephalitis resulting from sensitization to foreign protein (horse serum rabies vaccine pertussis vaccine) osteomyelitis scurvy acute multiple sclerosis pseudobulbar palsy myalgic meningoencephalitis (Iceland Tallahassee or Coventry disease) spinal epidural abscess or tumor neoplasms of the brain

too high because of the inclusion of cases of "nonparalytic poliomyelitis" many of which as pointed out above are instances of some other disease In *the writer's experience paralytic poliomyelitis may* be accompanied by a completely normal spinal fluid throughout its entire course but this occurs in no more than 0 5 per cent of cases In some patients decrease in number of cells in the spinal fluid is accompanied by a progressive rise in protein which may reach levels high enough to cause confusion with the cytoalbuminologic dissociation observed in infectious polyneuritis

Spinal Paralytic Poliomyelitis In the early stages of spinal paralytic poliomyelitis cramping pain in the muscles innervated by the affected neurones and hyperesthesia of the overlying skin are present The discomfort may be very severe muscle "spasm" the exact mechanism of which is not clear is usually detectable Paralysis may not appear for some time after the onset of symptoms In some instances increase in muscle weakness is very slow in others it becomes widespread within 48 hr Rarely a rapidly ascending paralysis of the Landry type is observed Age is one factor in determining the extent of involvement In children less than five years old paresis of one leg is most common In patients *between five and fifteen years of age weakness of* one arm or paraplegia is most frequent while in adults (sixteen to sixty five years old) quadriplegia is observed most often Dysfunction of the urinary bladder is at least ten times more frequent in adults than in children Paralysis of the muscles of respiration is most common in those older than sixteen years of age Infants younger than one year are subject to very extensive involvement Among adults men develop quadriplegia respiratory paral*ysis and loss of bladder function more frequently* than do women Pregnancy does not increase the severity of the disease unless parturition takes place during the acute phase There is a definite association of inoculation of antigenic materials ("triple vaccine" for example) with an increased risk of involvement of the muscles around the site of injection

The location of muscle weakness depends on the portion of the spinal cord affected Isolated infection of the cervical thoracic or lumbar areas may be present or two or more parts of the cord may be involved simultaneously The lumbar area is the one most frequently damaged

When the cervical portion of the spinal cord is involved there is paresis or paralysis of the muscles of the shoulders arms neck and diaphragm Very early in the disease the reflexes in the arms remain lively they diminish rapidly however and are usually absent by the time paralysis has become established Coarse twitching of the affected shoulder or arm muscles is common With cervical cord disease there is always danger of respiratory paralysis due to spread of the infection to the motor nuclei of the phrenic nerves and medulla

Weakness of the muscles of the chest upper portion of the abdomen and spine follows involvement of the thoracic portion of the spinal cord Difficulty in breathing results from dysfunction of the intercostal and other thoracic muscles The chest wall may be in "spasm" and may appear rigid despite the presence of only a minor degree of paresis Twitching of the thoracic abdominal or spine-supporting muscles may sometimes be noted

Disease of the lumbar portion of the spinal cord produces weakness of the muscles of the legs and inferior portions of the abdomen and back Again, pain tenderness "spasm" and twitching herald the oncoming paralysis and the reflexes are abolished with the development of flaccid paralysis Dysfunction of the iliopsoas muscles indicated by inability to sit up from a lying position the hip muscles quadriceps femoris hamstring and gastrocnemii, peroneals anterior tibials tensor fasciae latae glutei and sartorious may occur in various combinations In adults complete paraplegia is not infrequent Paralysis of the urinary bladder usually temporary occurs in about one third of patients over *sixteen years of age* and is rarely *observed in the* absence of weakness of the legs

The abdominal and cremasteric reflexes usually disappear before muscle weakness is marked in paralytic poliomyelitis and may be absent during the entire course of the disease An extensor plantar response (positive Babinski) has been elicited in a few cases during the first 1 or 2 days but is a rare finding its persistence or late development is incompatible with poliomyelitis Hyperesthesia of the *skin is frequent Sensory loss does not occur* Constipation abdominal cramps and meteorism are common in spinal paralytic poliomyelitis and are due to partial ileus resulting from involvement of the autonomic nervous system and weakness of the abdominal muscles When the disease is severe sympathetic nervous system disturbances with tachycardia hypertension abnormal sweating and cyanosis and coldness of the involved extremities not due to superficial vasospasm are present

Fever in spinal paralytic poliomyelitis is usually present for the first few days of the disease and disappears by lysis In about 90 per cent of cases there is little or no extension of paralysis after defervescence has been established for about 48 hr In about 10 per cent however progression of weakness may continue for as long as a week or more and may be of notable degree

Bulbar Poliomyelitis The incidence of bulbar poliomyelitis differs from one epidemic to another and varies between 6 and 25 per cent In patients subjected to tonsilloadenoidectomy within 30 days

take Attempts to control this problem consist of the liberal administration of fluids decrease of calcium intake acidification of the urine administration of salicylate and mobilization as early as possible

A syndrome resembling rheumatoid arthritis with redness swelling pain and tenderness of the larger joints is observed rarely in the convalescent phase of paralytic poliomyelitis A variety of skin rashes may occur including miliaria seborrhea and purpuric morbilliform or exfoliative eruptions due to drug sensitization Bedsores are common in respirator patients because of the difficulty in moving them about Markedly paralyzed individuals especially those whose life is threatened by respiratory difficulty frequently experience very difficult emotional problems Disorientation acute panic states Korsakoff like syndromes and acute psychoses have been noted Chronic anxiety and depression are almost universal in severely damaged adults and probably reflect merely the sudden impact of a crippling disease with its serious social and economic implications rather than brain damage due to viral invasion

Immunity

One attack of poliomyelitis usually confers a lifelong immunity against reinvasion by the same serotype Both neutralizing and complement fixing antibodies appear early in the disease the latter persist for only several years after infection while the former persist throughout life Theoretically individuals may suffer three episodes of the disease because immunity is strictly type specific Most adults and many children have poliomyelitis without paralysis or even nervous system invasion two or three times as shown by the presence in their serums of neutralizing antibody for more than one virus type This probably accounts for the decreasing frequency of the disease with increasing age There are however well documented instance of two episodes of paralyzing infection separated by a number of years in the same individual Infants may be protected against infection during the first three to six months of life by antibody passively transferred from the mother

Treatment

Cases of "abortive poliomyelitis even if recognized should receive no therapy except for symptomatic relief of the manifestations of the minor illnesses Antibiotics are without value

The management of nonparalytic poliomyelitis involves primarily the relief of the headache pain in the back and spasm" of the legs associated with meningeal irritation Rest in bed with the mattress supported by a board may be of importance in preventing paralysis and is helpful in reducing the back discomfort The application of wet heat in the form of hot packs" to the neck back and thighs produces considerable relief Analgesics such as Demerol and codeine are very useful and are preferable to other morphine derivatives Antimicrobial agents are useless because they have no effect on the primary disease and do not decrease the risk of secondary infection Neuromuscular examination should not be carried out more often than every 3 to 4 days Bed rest is terminated as soon as severe discomfort is absent in order to reduce the risk of phlebothrombosis and pulmonary embolism Every patient thought to have nonparalytic poliomyelitis should have careful assessment of muscle function and an orthopedic follow up study for 2 to 3 months after recovery The purpose of these measures is to detect and correct minor degrees of weakness which may become apparent only when muscles which appear normal at rest are taxed by the exertion of normal physical activity

The treatment of paralytic poliomyelitis involves (1) the use of all measures to spare the life of the patient threatened by involvement of vital areas, (2) relief of discomfort (3) maintenance of weak muscles in as good a condition as possible until normal neuronal function has sufficient time to return (4) immediate recognition and treatment of medical complications (5) prophylaxis and therapy of emotional disorders (6) surgical treatment of correctable defects and (7) social, economic occupational and physical rehabilitation

Patients with paralysis of swallowing loss of function of the breathing muscles pulmonary edema or shock are in great danger of death Dysfunction of the ninth and tenth cranial nerves while leading to complex problems of infection and regulation of caloric water and electrolyte balance is most important because of the danger of fatal obstruction of the airway For this reason it has been suggested that tracheostomy be performed in all such cases However thorough study has indicated that this operation is followed by a much higher incidence of bronchopulmonary infections due to organisms difficult to eradicate with antibiotic agents than occurs when the procedure is not carried out The preferred initial management of swallowing difficulty is postural drainage suction to keep the hypopharynx as free of fluids as possible and maintenance of adequate intake of food and water by nasogastric intubation The prone position takes advantage of the normal forward inclination of the trachea as an aid to drainage Elevation of the foot of the bed 2 to 3 ft from the floor also helps to keep fluids out of the lower respiratory tract Most important is judicious suctioning of the throat carried out by an experienced physician or nurse If in addition, fluid and electrolytes are administered parenterally at first and later by gavage

and spinal cord Coxsackie virus infection the encephalitis of the preicteric phase of infectious hepatitis infectious mononucleosis with neurologic involvement infections due to the enteric cytopathogenic human orphan (ECHO) viruses focal embolic *encephalitis associated with subacute bacterial* endocarditis tuberculous meningitis with hemiplegia or cranial nerve (especially the sixth) palsies and brain abscess Study of these diseases over a period of a few days to a week after onset clarifies the situation in most instances The only positive method of establishing the diagnosis of paralytic poliomyelitis is the isolation of the virus from the stool or pharyngeal secretions (spinal cord or brain at necropsy) and the demonstration of a rise in the level of neutralizing antibody to the isolated strain in acute and convalescent phase serums If virus cannot be isolated the three type strains maintained in tissue culture may be used a significant rise in titer of neutralizing antibody against a specific serotype is diagnostic

Medical Complications of Paralytic Poliomyelitis Paralytic poliomyelitis especially in adults often presents a number of serious and potentially lethal complications These complications occur most frequently when the respiratory muscles are involved *because of involvement of spinal or bulbar motor* neurones they are at times the direct cause of death Disturbances in water and electrolyte balance are common in patients receiving continuous artificial respiration Fever and the sweating which follows enclosure in a tank during the summer months together with vomiting diarrhea inability to take food and disturbances in carbon dioxide related to improperly regulated ventilation produce a series of chemical disturbances the repair of which taxes the ingenuity of the physician Edema and low electrolyte levels often follow overenthusiastic hydration and have been misinterpreted as *evidence of a salt wasting syndrome Myocarditis* is not uncommon in poliomyelitis it is probably due to direct viral invasion ECG changes mainly T and ST T and P R abnormalities are present in from 10 to 20 per cent of cases Interstitial infiltration of the myocardium with round cells and mild muscle changes are not infrequent and occurs in a few cases along with degenerative changes in muscle fibers Verrucous endocarditis involving the mitral valve has been described Severe myocardopathy has been thought to be responsible for death in some cases Hypertension may develop and is produced by two mechanisms (1) transient *elevation* of blood pressure due to hypoxia and (2) persistent hypertension secondary to *hypothalamic involvement* which may become malignant and lead to severe retinopathy convulsions and mental deterioration unless treated

Pulmonary edema and shock the exact pathogenesis of which is not known are usually the terminal events in fatal cases of poliomyelitis Although relatively young adults are involved phlebothrombosis of the legs with or without pulmonary embolism is not uncommon All methods of artificial *respiration* produce hemodynamic disturbances which are countered by reflex mechanisms acting to maintain normal blood pressure and cardiac output When patients are placed in respirators under *negative tank pressure (positive intratracheal* pressure) after hypotension and impending shock are already present the peripheral vascular collapse often is made worse Acute and marked dilatation of the stomach and large bowel perforation of the cecum acute ulceration of the duodenum stomach and esophagus the formation of multiple erosions of the entire gastrointestinal tract with considerable bleeding and paralytic ileus have been observed Marked depression of prothrombin with massive spontaneous hemorrhage occurs in individuals with severe poliomyelitis especially if they are receiving large doses of broad spectrum antibiotics orally Severe bulbar (ninth and tenth cranial nerves) or bulbospinal disease with paralysis of the breathing muscles is accompanied by the risk of major pulmonary atelectases Bacterial *infection is one of the most dangerous complications of* paralytic poliomyelitis Pneumonia is quite common in patients with paralysis of the muscles of respiration or deglutition The incidence of pulmonary infection is greatly increased by tracheostomy and is highest in the respirator case subjected to this operation The organisms involved most often are *Staphylococcus aureus* and gram negative bacteria such as *Proteus Pseudomonas pyocyanea Escherichia coli* and *Klebsiella pneumoniae* many strains of which are not sensitive to the commonly used antimicrobial agents *Chemoprophylaxis is without value in preventing secondary bronchopulmonary bacterial invasion*

The other common site of infection in poliomyelitis is the urinary tract which is exposed because of the necessity for chronic catheterization in patients with paralysis of the bladder chemoprophylaxis even when given together with tidal drainage is usually ineffective Although the symptoms may suggest only cystitis involvement of the kidney is always present The responsible organisms are those usually found in urinary tract infections and are often insusceptible to antibiotics and sulfonamides The renal problem is complicated by the freqeuncy of stone formation which may be responsible for renal colic obstruction of the pelvis and pyonephrosis increase in severity of pyelonephritis renal decompensation hypertension and vascular disease The factors which contribute to renal lithiasis in these cases are immobility with calcium mobilization *infection stasis dehydration and calcium in*

minimizes the possible effect of exercise in increasing the degree of paralysis Daily physiotherapy is usually started 3 to 4 days after complete defervescence has appeared and extension of weakness has stopped Exercise against resistance even that of gravity is thought to be most beneficial by some clinicians In many clinics exercise in water to remove the effects of gravity is standard practice

The physician must be constantly aware of the complications of paralytic poliomyelitis described above because their immediate recognition and treatment are often lifesaving The prevention and treatment of the emotional disorders which accompany severe paralytic poliomyelitis are often best carried out by the attending physicians and nurses Although the help of the psychiatrist is necessary in difficult situations the importance of physicians nurses and attendants who are in constant contact with the patients and are properly oriented towards these problems cannot be overemphasized

Maximal return of muscle function usually is established at the end of 2 years following the onset of paralytic poliomyelitis A review of the clinical problem by an orthopedic surgeon should be carried out if residual palsies remain and a program of surgical rehabilitation should be set in motion Persistent coldness and cyanosis of the lower extremities suggests consideration of lumbar sympathectomy

The impact of paralytic poliomyelitis on the social and economic status of adults is often very severe Every effort must be made to enlist the cooperation of social service agencies to minimize the disruptive effects of the disease Many patients require occupational rehabilitation because of inability to perform the work in which they were engaged prior to being crippled For others the use of devices such as movable splints hooks etc is very helpful in physical rehabilitation if this cannot be accomplished surgically

Prognosis

The over all mortality rate for poliomyelitis is about 5 per cent Patients with the abortive and nonparalytic types of the disease recover completely About 2 to 5 per cent of children and 15 to 30 per cent of adults (increasing with age) with paralyzing infection die When bulbospinal involvement especially with medullary or phrenic and intercostal nerve dysfunction is present the fatality rate varies between 25 and 75 per cent in these cases it is greatly influenced by age and the presence of shock pulmonary edema superimposed infection or other medical complications

Many persons with paralytic poliomyelitis recover completely In a considerable number there is return of muscle function to some degree Only a few remain totally paralyzed It is striking though paradoxical that the more life threatening the disease in the acute stage the more frequent is complete functional recovery if the patient survives Thus paralysis of the respiratory center usually disappears completely Dysfunction of the ninth and tenth cranial nerves is followed by total recovery in most instances although mild palatopharyngeal weakness may occasionally persist for life Paralysis of the muscles of respiration often disappears completely In some cases the final vital capacity although reduced is adequate to maintain ventilation even with moderate physical exertion In very few instances is chronic respirator care necessary Weak extremities regain about 60 per cent of the total strength that they will ever recover in 3 months and 80 per cent within 6 months Improvement may continue for as long as 2 years The final degree of functional return depends on the number of neurones totally destroyed it varies from as low as none to 10 per cent to as high as 100 per cent

Prevention

Because 90 to 95 per cent of cases of poliomyelitis are inapparent or minor infections and are not diagnosed the prevention of the disease by isolation is very difficult The common practice of isolating clinically evident cases is of much greater individual than public health benefit The usual period of isolation is about 2 weeks although virus may be present in the feces for a much longer period Contact with known cases should be avoided Restriction of community activities such as swimming gathering of people etc is not necessary except with large epidemics when it is more effective in allaying panic than in reducing infection Pregnant women should take special precaution because of the increased susceptibility to the disease during pregnancy Tonsillectomy is contraindicated in areas where poliomyelitis is present All individuals with minor illnesses during the poliomyelitis season should limit their physical activity and avoid chilling until all symptoms have disappeared

The use of gamma globulin prepared from pools of normal human plasma has not been strikingly effective as a prophylactic measure in either family or outside contacts However in persons peculiarly susceptible or in a vulnerable position such as pregnant women campers and physicians or nurses accidentally in contact with virus containing materials the administration of gamma globulin may be worthwhile The dose is 0 15 ml per lb body weight the total quantity for adults is 20 ml

Active immunization against paralytic poliomyelitis has been successfully produced by parenteral administration of formalin inactivated strains of the three viral serotypes grown in monkey kidney

most patients have little or no difficulty in this respect In some cases however tracheostomy becomes necessary despite the risks The indications for this operation are (1) abductor paralysis of the vocal cords confirmed by indirect or direct laryngoscopy—this makes the operation mandatory (2) pneumonia with inability to clear the lungs of exudate the opening in the trachea permits easy drainage of the lower airway (3) repeated bouts of major degrees of pulmonary atelectasis requiring tracheal catheterization or bronchoscopy (4) inability to keep the airway relatively free of secretions—this is often purely a matter of availability of a sufficient complement of experienced personnel Using these indications few tracheostomies have been performed in the writer s clinic

The development of respiratory muscle paralysis demands early recognition and treatment Decreased movement of the diaphragms or intercostal *muscles or both indicates the need for frequent* determination of vital capacity When this is reduced to 50 per cent of normal or less on the basis of age and weight artificial respiration must be given with a tank or cuirass type of chest respirator The patient should be informed of the fact that he is to receive this type of treatment and instructed to relax and synchronize as well as possible his breathing with that of the machine The level of negative pressure employed is that which produces a normal tidal volume as measured with a respirometer Arbitrary setting of negative pressures is useless and potentially dangerous because two patients with the same body area and equal decrease in vital capacity often require different negative intratank pressures to produce normal tidal volumes The speed of respiration is adjusted to 12 to 16 per minute and is altered if necessary to suit the comfort of the patient Determinations of plasma CO content and arterial oxygen saturation should be made frequently especially when bulbar disease with pooling of secretion is present because a considerable degree of hypoxia may develop before cyanosis is apparent It is best to administer oxygen to all patients requiring artificial respiration If hypotension is present alternating negative and positive pressures of equal degrees often help in restoring blood pressure to normal level The tank respirator is preferable to the chest type because at the same level of negative pressure it produces a greater degree of ventilation The rocking bed is not an adequate substitute for the tank in the acute stage of respiratory paralysis The electrophrenic respirator is of no value in the management of paralysis of the muscles of respiration because as a result of rapid axonal degeneration the phrenic nerves often fail to respond to stimulation within 24 to 36 hr following onset of the disease The use of antimicrobial agents to prevent secondary bacterial infections in bulbar and respiratory muscle paralysis with or without tracheostomy is *not* beneficial and may in fact be dangerous "Weaning" from the tank respirator should be started after the first day and accelerated as rapidly as possible

The use of the electrophrenic respirator is indicated when the respiratory center is involved Tank respiration may actually increase this type of difficulty Indirect stimulation of one phrenic nerve through the skin is usually sufficient If the need for the electrophrenic respirator is continuous for several days or more the phrenic nerve may be exposed and the electrode applied directly by means of a metal clip

The treatment of infections of the lungs and urinary tract which complicate paralytic poliomyelitis is the same as that employed in these types of disease without nervous system infection The frequency of involvement of antibiotic insensitive or*ganisms necessitates determination of resistance* of the isolated bacteria to a variety of antimicrobial drugs

There is no specific treatment for poliomyocarditis When pulmonary edema supervenes in patients receiving artificial respiration the use of positive intratank pressure or positive pressure breathing through a cuffed tracheotomy tube may be helpful Shock is easier to prevent than to treat Assurance of adequate oxygen saturation prevention of dehydration and early treatment of superimposed bacterial infection are of prophylactic value When marked hypotension develops vasoconstricting agents such as norepinephrine are often very helpful in establishing normotension As a rule however these drugs finally become ineffective as their use is prolonged Plasma infusions may be of some help Hypotension appearing during artificial respiration may respond to alternating positive and negative tank pressures of approximately the same degree

The relief of discomfort is one of the most important problems in the care of paralytic poliomyelitis Hot wet packs diathermy warm baths and dry heat reduce pain due to muscle spasm " Analgesic drugs should be used whenever necessary but morphine derivatives should be avoided Changing the position of paralyzed limbs and moving the patient about in bed are effective in reducing the frequency and intensity of pain

Weak muscles must be maintained in as good condition as possible until neural function returns the time degree and extent of resumption of function are unpredictable but treatment should be continued for at least 2 years This aspect of therapy is best managed by the physiotherapist who has had experience with poliomyelitis Muscle examinations should not be carried out too often in the acute phases of the disease this precaution

The term *street virus* is used to designate the agent of the naturally occurring disease *Fixed viruses* are rapidly multiplying strains used in vaccine production which have lost their infectivity for salivary gland tissue after passage in laboratory animals There is only one antigenic type of the virus

Epidemiology All mammals are potential vectors but carnivores are responsible for most cases in man and animals Virus is present in saliva for several days before symptoms develop and persists until the time of death Rabies is usually contracted from bites occasionally from scratches or abrasions contaminated with infected saliva or rarely by penetration of mucous membranes The principal source of infection in man is the dog but 5 to 15 per cent of human cases are caused by cats or other animals The usual form of the disease in dogs called *furious rabies* is characterized by progressive agitation aimless wandering difficulty in swallowing frothing at the mouth labored respirations feeble bark ataxia convulsions and vicious indiscriminate attacks on all creatures and inanimate objects Paralysis and stupor usually develop 2 to 3 days before death and are the sole manifestation (*dumb rabies*) in about one fifth of infected dogs

Although quarantine killing of stray animals and vaccination are effective in controlling canine rabies large reservoirs of infection exist in wild animals such as the wolf in Eastern Europe and Western Asia the jackal in India and North Africa and the mongoose in South Africa Human and canine rabies caused by bites of rabid foxes is not unusual in the United States and the disease is also found in skunks raccoons coyotes squirrels bobcats mountain lions and other mammals Vigorous control measures have eliminated all foci of rabies in domestic and wild animals of Scandinavia and the British Isles and prevented importation of the disease into Hawaii and Australia

The vampire bat transmits a paralytic form of the disease to cattle and horses and constitutes an important reservoir of rabies in South and Central America Mexico and the West Indies Vampire bats are occasionally nocturnal predators of man attacking silently to take their blood meal without the sleeping victim s knowledge Human rabies acquired from bites of common bats was first recognized in the United States in 1951 to 1953 and subsequent surveys have revealed that the disease occurs in many insectivorous and fructivorous species Isolation of rabies virus from bats was also reported from Yugoslavia in 1956 There is evidence to suggest that bats are the original hosts and constitute the largest reservoir of rabies

Rabies is almost invariably a rapidly fatal infection in all mammals except the vampire bat which can continue to transmit the disease for many months Sudden unprovoked attacks by any animals are rare and should be considered as presumptive evidence of exposure to rabies Human to human transmission is exceedingly rare

Pathogenesis Rabies virus spreads from the site of inoculation along sensory nerve pathways to the posterior columns of the spinal cord if the bite is on the extremities or trunk or by cranial nerves to the brain stem from face wounds The salivary glands intestine pancreas renal tubules and adrenal medulla are involved by extension along the autonomic nerves Viremia may occur Focal inflammation neuronophagia demyelinization hemorrhages and perivascular infiltration by mononuclear cells occur throughout the nervous system but these changes are most marked in the basal ganglions subcortical areas and spinal cord Rabies can be distinguished from other viral encephalitides only if the pathognomonic Negri bodies are found These are eosinophilic inclusion bodies 0 5 to 10 μ in diameter demonstrable in the cytoplasm of nerve cells by special stains In all animals including man they are found in greatest abundance in Ammon s horn of the hippocampus and to a lesser extent in pyramidal cells of the cerebral cortex Purkinje cells of the cerebellum and nuclei of the basal ganglions

Manifestations The *incidence* of rabies in unvaccinated individuals bitten by rabid animals is about 15 per cent but varies from 5 to 70 per cent depending on the amount of virus in the saliva and the location and depth of the wounds It may be difficult to obtain a history of animal exposure if the disease is acquired from minor bites or scratches The *incubation period* is usually 30 to 70 days but can be as short as 10 days or rarely more than a year Short incubation periods occur after face or arm bites multiple wounds or wolf bites Prodromal symptoms of fever of 100 to 102 F headache malaise nausea vomiting sore throat and persistent loose cough are often present for 1 to 4 days The most significant early manifestations in about 80 per cent of cases are tingling paresthesias and dull or stabbing pain at the site of the bite often radiating to the hip shoulder or neck and to distal parts of the involved extremity The wound may be inflamed and excoriated by the patient s scratching The first or *excitement* phase of the disease is characterized by increasing agitation marked restlessness excessive motor activity aimless pacing dysarthria and occasionally visual or auditory hallucinations Episodes of unreasoning fear and rage alternate with profound depression The patient may become destructive wildly apprehensive and combative if restrained but usually does not attack his attendants Spasmodic gross muscle contractions and generalized clonic or tonic convulsions with opisthotonos develop shortly after the onset often precipitated by loud noises bright

tissue culture The vaccine is about 60 to 70 per cent effective against type 1 and 85 to 90 per cent against types 2 and 3 The recommended schedule of inoculation is 1 ml initially followed by 1 ml 4 weeks and 7 months later No antibody is demonstrable in about 20 per cent of patients after the first injection In most individuals without antibody prior to vaccination neutralizing capacity of low degree appears in about 4 to 6 weeks after the first dose of vaccine but falls gradually over the next few months The booster injection 7 months later produces a rapid rise in antibody to high levels Persons immune to a single serotype when first inoculated develop a rapid increase in antibody to all three types

The vaccine does not appear to decrease the incidence of nonparalytic poliomyelitis The duration of protection is unknown Reactions to the vaccine are uncommon headache stiffness of the neck arms and legs which may be accompanied by pain skin hypersensitivity fever sore throat vomiting and pain at the site of injection have been noted Approximately one to three paralytic cases of poliomyelitis appear to be associated with each million injections of vaccine

Experimental studies suggest that immunization with orally administered living virus vaccines produces neutralizing antibodies and protection against infection The strains of poliomyelitis virus used are capable of growing in the intestinal tract but do not invade the nervous system Adequate field trials have not yet been carried out Although the effects of this type of vaccine are promising judgment as to the degree of effectiveness must be reserved

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179 RABIES

Robert R Wagner

Definition Rabies (hydrophobia lyssa) is a fatal viral infection of the nervous system transmitted in saliva of rabid animals

History Some of the earliest extant writings contain suggestive references to mad dogs Aristotle (c 335 B C) described the transmission of rabies from dogs to other animals and Celsus (c A D 100) recognized that hydrophobia in man was caused by the bite of a rabid dog The prevalence of the disease in man increased markedly in the eighteenth century following a European epizootic of canine rabies The first effective control measures were instituted in Scandinavia resulting in elimination of the disease there by 1826 Galtier s report in 1879 of transmission of rabies to laboratory rabbits led to the classical studies by Pasteur and his associates of fixed" virus for vaccine production Histologic diagnosis of infection became possible after Negri in 1903 described the characteristic cellular inclusion bodies of the disease

Etiology Rabies virus is infectious for nervous tissue of all warm blooded animals and can also be grown in tissue culture and chick embryos It is rapidly destroyed by heat drying and formalin but can be preserved in glycerol or by freezing

days No treatment is required if the animal remains healthy Immune serum should be administered within 24 hr to all individuals who incur severe or multiple bites regardless of whether the animal shows signs of rabies at the time Every bat bite should be considered to be an exposure to rabies

No specific treatment is available if clinical manifestations develop The patient should be kept in a quiet darkened draftless room and disturbed as little as possible Large doses of barbiturates are more effective than opiates in lessening anxiety delirium and the frequency of pharyngeal spasms and convulsions Parenteral administration of fluids is often required

Prognosis Thus far rabies has been an invariably fatal disease in man However every patient should receive all possible supportive treatment in the hope that the diagnosis is in error

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180 HERPES ZOSTER

Lewis L Coriell

Definition Herpes zoster also called *shingles* or *zona* is an acute infectious disease of man It is caused by a virus and characterized by unilateral segmental inflammation of the posterior root ganglions or extramedullary ganglions of cranial nerves and by a painful vesicular eruption of the skin along the *peripheral distribution of the involved nerve*

History The disease was called *zona* (a girdle) by the Greeks because of the bandlike distribution of the eruption about the trunk Bokay (1888) suggested a possible etiologic relationship between zoster and varicella and Lipschutz (1921) defined the specific histopathology of the skin lesions Successful transfer by inoculation of vesicle fluid into *human subjects was first reported by* Kundratitz (1925)

Etiology The virus of herpes zoster is a relatively large virus (204 by 240 μ) It is a strict parasite of man Electron micrographs of vesicle fluid have shown the virus to be similar in size and shape to the virus of varicella The virus may be plentiful in early vesicles but is typically scanty after 24 hr The absence of a susceptible laboratory animal has *hindered immunologic studies*

Epidemiology Infection is less common in children *and increases in frequency severity and duration* with advancing age It occurs at all seasons of the year and is slightly more frequent in males than in females In the United States the majority of but not all patients with herpes zoster give a history of a previous attack of varicella in childhood Epidemics have occurred in schools and barracks but are not common Outbreaks of herpes zoster have occurred in contacts of a patient with varicella and vice versa The grouping of these secondary infections suggests that zoster is infectious only during *the first 2 or 3 days after appearance of the eruption* Secondary zoster following trauma such as spinal puncture administration of arsenic or bismuth spinal cord tumor tabes and lymphatic leukemia have suggested the possibility that the virus may remain dormant in the tissues over long periods of time The disease is more common in persons who are overworked or ill On the basis of the evidence available the viruses of herpes zoster *and varicella are closely related if not identical and* it is tempting to explain the various clinical manifestations by postulating one virus which causes different diseases in the susceptible and the partially immune subject Final solutions of this problem must await the development of new laboratory techniques

Pathogenesis Whether the virus enters the skin and travels up the sensory nerve or extends peripherally *is purely a matter for conjecture at the present* time The virus has been demonstrated only in the skin lesions although an inflammatory reaction is a constant finding in the segmental nerve its sensory ganglion and the posterior horn of the spinal column (posterior poliomyelitis) The regional lymph nodes show an acute inflammatory *reaction The* anterior horn the meninges and the brain may be involved The histologic central nervous system lesions *are infiltration with small round*

lights touch or even drafts Respirations become shallow and irregular the pulse rapid and thready and the temperature usually exceeds 103 F There may be involvement of the autonomic nervous system manifested by dilated irregular pupils excessive lacrimation sweating and salivation Many *patients also exhibit vertigo nystagmus optic neuritis* with central blindness diplopia strabismus or facial palsy Paralysis of the vocal cords results in hoarseness or aphonia Hyperactive deep tendon reflexes Babinski signs and nuchal rigidity are often present

The most characteristic feature of the disease is severe painful *contractions of the pharyngeal muscles* initially *precipitated by attempts to swallow* fluids This usually develops 1 to 3 days after onset and progresses until the mere sight sound mention or even thought of water cause reflex spasms of the muscles of deglutition and respiration leading to bouts of apnea cyanosis and generalized convulsions Most patients manifest a *fear of water (hydrophobia)* and to avoid swallowing allow *frothy saliva to drool from the mouth Death usually* follows a generalized convulsion with prolonged apnea

Patients who survive the excitement stage of the *disease develop generalized flaccid paralysis* often evident at first in the bitten extremity Muscle spasms and pharyngeal contractions cease and agitation gives way to depression apathy hyporeflexia and coma The ability to swallow may return temporarily and there is often transient slowing of the pulse and respirations The bladder usually becomes atonic Generalized paralysis resembling the Guillain Barré syndrome is occasionally the only neurologic manifestation Rabies acquired from vampire bats which frequently bite the toes usually takes the form of Landry s ascending paralysis without excitation or pharyngeal spasm Death usually occurs 2 to 3 days after onset of paralytic rabies but may be delayed for several weeks

Laboratory Findings The blood leukocyte count may be elevated occasionally to 30 000 cells per cubic millimeter with an increased number of polymorphonuclear and large mononuclear cells Glycosuria acetonuria proteinuria and oliguria are present in most cases The cerebrospinal fluid is usually normal but may contain slightly increased amounts of protein and as many as 100 mononuclear cells per cubic millimeter Virus may be present in saliva or rarely in cerebrospinal fluid Serum antibodies can be determined by neutralization or complement fixation tests but serologic studies are of little value because all surviving patients have received vaccine or immune serum Definitive diagnosis is usually made at autopsy by demonstrating Negri bodies or by isolation of virus from the brain

Differential Diagnosis *Hysterical reactions* to dog bites and *allergic encephalomyelitis* caused by rabies vaccine are sometimes difficult to differentiate from rabies Paralytic rabies may be confused with poliomyelitis or the *Guillain Barré syndrome* particularly when a history of animal bite cannot be *obtained or the incubation period exceeds 3 months* Many of the manifestations of *tetanus* except trismus resemble those of rabies *Delirium tremens* and *intoxication with belladonna alkaloids* occasionally simulate rabies

Treatment The basic principle in the treatment of individuals exposed to rabies is to furnish sufficient antibody to prevent the virus from reaching *the central nervous system Semple s vaccine* prepared from fixed virus grown in rabbit brain and inactivated with phenol is commonly used for this purpose in the United States A course of 14 daily inoculations is recommended A potent vaccine free of brain tissue can be prepared in chick embryos from the Flury strain of rabies virus It produces high antibody titers in man and has proved to be *effective for vaccination of dogs and cattle* Passive immunization with antirabies horse serum used as an adjunct to vaccination appears to afford enhanced resistance to infection particularly in heavily exposed individuals The local treatment of bites consists of thorough cleaning with strong soap or detergent solutions and infiltration of the area with immune serum Cauterization or debridement of the wound is no longer recommended

The chief hazards of Semple s vaccine are *hypersensitivity reactions* with severe local erythema, often accompanied by fever and arthralgia in about 5 per cent of cases and *peripheral neuritis* or *allergic encephalomyelitis* caused by the rabbit brain tissue in 1 of 2 000 to 10 000 vaccinated individuals Encephalomyelitis usually occurs 1 to 3 weeks after the first injection of vaccine and is characterized by the sudden onset of chills fever headache and vomiting followed by disorientation dysarthria ataxia paresthesias cranial nerve palsies visual disturbances and frequently hemiparesis or paraplegia Increased concentrations of protein in the cerebrospinal fluid and mononuclear pleocytosis are noted in the majority of cases The mortality rate varies from 0 to 25 per cent and about one third of recovered patients have residual *neurologic* disorders

The decision to proceed with antirabies treatment must depend on the risk of exposure in individual cases Vaccine should be administered promptly if a person is bitten by an animal that escapes is clinically rabid or shows histologic evidence of infection Healthy dogs or cats that inflict minor bites or scratches contaminated with saliva should be impounded and observed for 10

ophthalmic involvement both oral and local antibiotics have been recommended but the choice of antibiotic in this serious complication should be guided by bacterial cultures and sensitivity tests Local treatment of lesions of the globe of the eye should be supervised by an ophthalmologist Early relief of pain and inflammation following cortisone and corticotropin has been reported in a few uncontrolled cases Transfusions of whole blood from persons who have recently recovered from herpes zoster has been abandoned in most clinics In this self limited disease therapeutic regimens based on a small number of observations are apt to be unreliable Severe postherpetic pain may be resistant to all types of management One theory advanced to explain this is the activation of self contained pain circuits in and above the thalamus The following procedures are based on the supposition that the defect is central injection of dorsal root ganglion with alcohol or irradiation with x ray dorsal rhizotomy cordotomy and lobotomy On the theory of peripheral nerve abnormality is based vitamin B therapy procainization or excision of skin, surgical Pituitrin paravertebral block intravenous tetraethylammonium chloride and sympathetic ganglionectomy Other empirical procedures which have also been helpful in certain cases include autohemotherapy sodium iodide moccasin venom and Protamide The multiplicity of recommended procedures is eloquent evidence that none is entirely satisfactory

Prognosis It is very unusual for serious complications to follow inflammation of the spinal ganglions Partial paralysis of the third fourth sixth and seventh cranial nerves or hypesthesia may persist for some time Significant impairment of vision occurs in a high percentage of cases of zoster ophthalmicus

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181 MUMPS (Epidemic Parotitis)

Robert G Petersdorf and Ivan L Bennett Jr

Definition Mumps is an acute communicable disease of viral etiology characterized by painful swelling of the salivary glands the gonads meninges and pancreas are sometimes involved

History Epidemic parotitis was described by Hippocrates The disease was produced experimentally in cats by Wollstein in 1918 but it was not until 1934 that its viral etiology was established by Johnson and Goodpasture Habel found in 1945 that the virus could be propagated in the chick embryo and Enders demonstrated complement fixing antibody in the serum of patients convalescent from mumps

Etiology The causative agent of mumps is a virus of intermediate size that closely resembles the influenza viruses in its properties It can be cultivated in the chick embroyo and will agglutinate chicken erythrocytes Mumps virus does not show the tendency to antigenic variation that is characteristic of influenza virus

Epidemiology Mumps is world wide in distribution It is endemic in urban communities although small epidemics frequently occur in settings such as schools camps and barracks Approximately 90 per cent of city dwellers and only 10 per cent of the rural population have been infected Data gathered from complement fixation and skin tests as well as experimental infections in volunteers suggest that at least 40 per cent of human infections are unapparent Man is the only reservoir Infection is transmitted by droplets or fomites The virus is present in saliva and blood for several days before symptoms occur and can persist in salivary secretions for 10 days after the onset of parotid swelling From a practical point of view therefore patients should be isolated until the parotitis has subsided

cells hemorrhage destruction of ganglionic nerve cells and secondary gliosis

The skin vesicle is confined to the epidermis while the corium is congested and infiltrated with inflammatory cells In the margin of the vesicle are epithelial cells undergoing balloon degeneration some of which contain eosinophilic intranuclear inclusion bodies which displace the basichromatin to the periphery of the enlarged nucleus Multinucleated giant cells may be present each nucleus containing an inclusion body Within 2 or 3 days inflammatory cells fill the vesicle and healing progresses from below frequently with slight scarring

Manifestations The incubation period varies from 7 to 21 days A preeruptive and posteruptive stage are distinguished The preeruptive stage consists of fever and constitutional symptoms with pain paresthesias or hyperesthesia over the segmental distribution of the involved nerve for 2 to 4 days Following this an erythematous dermatitis appears which quickly becomes papular and vesiculates with large or small grouped vesicles on an erythematous base The vesicles at first clear become cloudy within 2 to 3 days then crust and dry after 5 to 10 days The eruption may appear first near the spinal column with successive crops over the distal distribution of the nerve The pain and the vesicular band following radicular lines run transversely around the trunk and vertically over the arm and leg The lesions are almost always unilateral Headache and meningismus are not uncommon Pain is frequently slight or absent in young children but may be intense and not completely controlled by analgesic drugs in adults It is variously described as aching soreness burning gnawing shooting stabbing or neuralgic

The regional lymph nodes are enlarged and tender Secondary bacterial infection of the ruptured vesicles is common Over 75 per cent of cases occur between the second dorsal and second lumbar vertebrae and rarely below the elbow or knee Involvement of the fifth cranial nerve is next in frequency and in 50 per cent the globe of the eye is affected When the nasociliary branch of the gasserian ganglion is involved the cornea sclera or ciliary body may be permanently damaged the first branch of the fifth nerve is affected more frequently than the second or third Disease of the geniculate ganglion may lead to zoster of the concha of the ear or the external auditory canal the soft palate and loss of taste (Hunt s syndrome) this is often accompanied by paralysis of the seventh nerve Paralysis is not uncommon in cephalic and cervical zoster but is rare in zoster of the trunk only 44 cases having been reported up to 1943 Second attacks are exceedingly rare and should suggest an alternate diagnosis of localized herpes simplex In some patients a generalized vesicular eruption simulating varicella appears shortly after the appearance of the localized lesion (zoster generalisata)

The total course of the disease from onset to complete recovery is 10 days to 5 weeks Burgoon observed that in the age group up to nineteen years 90 per cent cleared within 14 days while in the forty to fifty nine year age group 45 per cent cleared in this interval If the vesicles all appeared within 24 hr the total illness was short and if crops of vesicles appeared up to 7 days then the total duration was progressively longer A serious complication is the syndrome of postherpetic neuralgia which is limited to the aged with arteriosclerosis It usually involves only the trunk or the ophthalmic division of the trigeminal nerve Frequently there is an interval between the acute phase and full unfolding of severe pain which may be described in various ways by individual patients but is of such persistence and intensity that the patient cannot rest or sleep Pain may persist for weeks or months

Laboratory Findings The fluid from unruptured vesicles is sterile bacteriologically The cerebrospinal fluid is abnormal in 40 per cent of cases pressure may be increased and a pleocytosis of up to 300 mononuclear cells has been observed

Differential Diagnosis In the preeruptive stage the diagnosis is difficult and the disease is usually confused with many other more common causes of pain such as pleurisy appendicitis "lumbago pleurodynia or collapsed intervertebral disk After the unilateral eruption appears the clinical features are so characteristic that diagnosis is simple Occasionally localized herpes simplex along the distribution of a segmental nerve may simulate zoster including the localized pain and tenderness Herpes simplex infection can be confirmed in the laboratory (see Chap 185 p 1091)

Treatment *Treatment is directed at increasing* the patient s comfort and preventing secondary infection The average case of herpes zoster is self limited and presents no serious complications The two unsolved problems are the syndrome of postherpetic neuralgia and ophthalmic zoster In the acute phase pain is usually controlled by aspirin and codeine combined with mild sedation Local anesthetic ointments are not very effective in controlling pain A petrolatum gauze pad bandage to prevent painful trauma by clothing may be helpful The skin lesions are adequately managed with applications of *calamine lotion in most cases* Application of adhesive tape strapping for the preeruptive pain of herpes zoster should be avoided as it will lead to extensive loss of epidermis upon removal of *the tape Antibiotics* have no effect on the virus but may be indicated to control secondary infection particularly in ophthalmic zoster or severe spinal involvement with secondary infection In

increased pressure The protein content is moderately elevated and glucose and chloride are normal In a small proportion of cases however significant lowering of cerebrospinal fluid glucose occurs and this may persist for several days

Usually mumps meningoencephalitis runs its course in a week and leaves the patient without disability The commonest serious residual disability is nerve deafness which fortunately is rare and when it does occur is likely to be unilateral

Rarer Manifestations Inflammation of the lacrimal gland thymus thyroid breast and ovary can occur *Oophoritis* is difficult to diagnose with certainty but can be suspected if lower abdominal pain and fever persist Sterility has never been reported as a complication of mumps oophoritis *Vulvovaginitis uveitis* and *iridocyclitis* have been reported in mumps but it is difficult to be sure that they are caused by the virus *Myocarditis* as evidenced by transient electrocardiographic abnormalities occurs in about 15 per cent of cases but clinical evidence of impaired cardiac function is virtually unknown *Splenomegaly hepatomegaly* and transient *icterus* are seen but are rare and of little significance

A rare but interesting late complication is mumps *polyarthritis* The onset of arthritis is 1 to 2 weeks after convalescence begins and it usually subsides within 6 weeks without residual joint damage

Laboratory Findings In uncomplicated parotitis the blood leukocyte count is normal although a mild leukopenia with a relative lymphocytosis can occur Complications notably orchitis are often accompanied by polymorphonuclear leukocytosis with counts as high as 30 000 per cubic millimeter In meningoencephalitis the blood leukocyte count is ordinarily within normal limits The erythrocyte sedimentation rate is usually normal but often rises with the onset of testicular or pancreatic disease As has been mentioned the serum amylase is elevated in salivary adenitis and pancreatitis serum lipase is elevated only in pancreatitis which can also be accompanied by hyperglycemia and glycosuria

The cerebrospinal fluid contains 0 to 2 000 cells per cubic millimeter predominantly mononuclear The severity of neurologic symptoms bears no relation to the extent of pleocytosis

Transient bilirubinemia and derangement of tests of liver function occur in some patients with mumps but the true incidence of these findings has not been subjected to careful study

The serum complement fixation test becomes positive during the second week of disease and remains so for about 6 weeks Inhibition of viral hemagglutination by convalescent serum is demonstrable later and persists for several months These serologic tests are necessary only in atypical cases or instances of "aseptic meningitis"

Injection of inactivated virus intradermally produces a delayed reaction of the tuberculin type in immune individuals The skin test if positive early in the course of an illness suspected of being mumps is a strong argument against the diagnosis However because skin reactivity appears about 4 weeks after infection and also because the intradermal administration of antigen can stimulate antibody production and make interpretation of complement fixation tests difficult, the procedure is rarely indicated for diagnostic purposes

Diagnosis The diagnosis of mumps during an epidemic is usually obvious Sporadic cases however must be distinguished from other causes of parotid enlargement *Bacterial parotitis* is still seen as a complication in debilitated patients postoperatively and in advanced uremia With suppuration which is common pus can be expressed from the ducts and striking polymorphonuclear leukocytosis occurs *Calculus* in a salivary duct usually detectable by palpation can give painful swelling of the gland *Drug reactions* can produce tender swellings of the parotid and other salivary glands "Iodide mumps is the commonest type mercurialism can also produce this picture Careful history usually serves to clarify the etiology of these reactions *Cervical adenitis* caused by streptococci bull neck diphtheria infectious mononucleosis or cat scratch disease *sublingual cellulitis* (Ludwig s angina) and *cellulitis of the external auditory canal* are usually easy to distinguish from mumps by careful examination Swelling of the parotid produced by *tumor* is usually of long standing The common "mixed tumor" of the parotid is well circumscribed nontender and very firm almost cartilaginous on palpation Parotid swelling and fever often accompanied by lachrymal adenitis and uveitis ("Mikulicz s syndrome") can occur in *tuberculosis leukemia Hodgkin s disease* and *lupus erythematosus* The onset may be sudden but the process is usually painless and lasts for weeks or months "*Uveoparotid fever*" of similar type can be the first manifestation of sarcoidosis however the process in this disease is frequently accompanied by single or multiple palsies of cranial nerves and is referred to as *Heerfordt s syndrome* Finally there is a "primary" type of chronic inflammation of the parotids and other salivary glands often associated with atrophy of the lachrymal glands that occurs most commonly in women past the menopause With cessation of lachrymal and salivary function there may be striking dryness of the conjunctiva cornea (keratoconjunctivitis sicca) and mouth (xerostomia) A variety of systemic manifestations including arthritis of the rheumatoid type has been re

The disease occurs most commonly between the ages of five and fifteen although the age range of reported cases is one to ninety nine years The illness is extremely rare outside the age group of four to forty In Europe and the United States seasonal peaks in incidence occur in the winter and spring

One attack of mumps confers lasting immunity second attacks are exceedingly rare Immunity is just as solid after unilateral as after bilateral parotid involvement

Pathogenesis The upper respiratory tract is the portal of entry and the initial site of multiplication of the virus After an incubation period ranging from 8 to 28 and averaging 18 days virus enters the blood and is widely distributed The salivary glands testes and meninges most commonly show evidence of infection more rarely the pancreas ovary breast thyroid thymus heart liver and cranial nerves are involved

Manifestations *Salivary Adenitis* Parotitis may be preceded by a prodromal period of malaise anorexia chilly sensations feverishness and sore throat Two early findings that suggest the correct diagnosis are tenderness when upward pressure is exerted on the angle of the jaw and reddening and pouting of the orifice of Stensen s duct In many cases the first indication of illness is parotid swelling Usually swelling of one gland is followed within 4 or 5 days by contralateral involvement in about one third of the cases parotitis remains unilateral Swelling of the submaxillary and sublingual salivary glands is common but is often overlooked The enlarged parotid extends from below the ear to the lower portion of the ramus of the mandible and to the inferior portion of the zygomatic arch The skin over the gland may be red and taut Considerable pain and tenderness are present and eating swallowing and talking cause marked discomfort There is swelling and erythema of the orifice of Stensen s duct but no purulent discharge is expressible Sublingual and submaxillary adenitis sometimes give rise to edema of the anterior neck which can extend into the presternal region edema of the glottis can also occur and on rare occasions necessitates tracheotomy

Salivary gland enlargement is maximal in 2 or 3 days and gradually subsides during the ensuing week It is usually associated with malaise headache anorexia and fever of 100 to 103 F However systemic manifestations are sometimes mild or absent particularly in children

Orchitis Mumps is complicated by orchitis in 18 to 20 per cent of postpubertal males This manifestation of the disease usually appears 7 to 10 days after the onset of salivary adenitis although it may precede it or appear simultaneously occasionally orchitis occurs in the absence of parotitis Testicular involvement is unilateral in approximately 75 per cent of patients

Orchitis is usually heralded by recrudescence of malaise and appearance of chilly sensations headache nausea and vomiting True rigors and fevers of 103 to 106 F are frequent The testis becomes greatly swollen and painful The epididymis is often palpable as a swollen tender cord prostatitis and seminal vesiculitis are also common Swelling pain and tenderness persist for 3 to 7 days and gradually subside defervescence parallels subsidence of testicular inflammation Occasionally the fever falls by crisis

Atrophy of the involved testes occurs in at least half the cases and may be apparent within 2 weeks after the acute episode Even after bilateral orchitis sterility is distinctly unusual An association of pulmonary infarction with mumps orchitis has been noted and it has been suggested that thrombosis of veins of the prostatic plexus secondary to the inflammatory process gives rise to emboli

Pancreatitis This is a relatively uncommon but potentially serious complication of mumps Pancreatitis should be suspected in a patient who has abdominal pain radiating to the back tenderness, nausea vomiting and constipation Occasionally a mass can be palpated in the epigastrium or left upper quadrant Peripheral vascular collapse is a rare but ominous complication Serum and urinary amylase are elevated in mumps pancreatitis but are not diagnostic in the presence of salivary adenitis If the parotid swelling has subsided however elevation of serum amylase is indicative of pancreatic inflammation Transient hyperglycemia and glycosuria as well as steatorrhea occur but chronic diabetes mellitus and pancreatic insufficiency are very unusual

Central Nervous System Involvement Involvement of the central nervous system in mumps is common as evidenced by the occurrence of cerebrospinal pleocytosis in nearly 50 per cent of cases Symptoms of severe headache nuchal rigidity and drowsiness occur in only one patient in ten, however severe meningoencephalitis with coma delirium convulsions and cranial nerve palsies is unusual

Meningeal involvement is usually preceded by parotitis but can be the first manifestation or often the only manifestation of infection by mumps virus Indeed serologic studies indicate that 10 to 15 per cent of cases of "aseptic meningitis" in this country are caused by mumps virus For some unexplained reason symptomatic involvement of the central nervous system is three to five times more common in males than in females

The cerebrospinal fluid is clear and under slightly

Section 16 Other Viral Infections

182 YELLOW FEVER

W Elizabeth Gambrell

Definition Yellow fever is an acute infectious disease caused by a virus and transmitted to man by the bite of an infected mosquito Its chief characteristics are fever jaundice bradycardia proteinuria and a hemorrhagic tendency The infection may be mild and almost asymptomatic or extremely severe and rapidly fatal Two types of the disease are now recognized *urban yellow fever* transmitted from man to man by the bite of the mosquito *Aedes aegypti* and *sylvan* or *jungle yellow fever* transmitted to man from an animal reservoir (monkeys) by other species of forest mosquitoes

Etiology The virus of yellow fever is small its size being estimated at 17 to 28 mμ It can be inactivated easily by heat and ordinary antiseptics but can be preserved for months in 50 per cent glycerin and for years in the desiccated refrigerated state Two general types are recognized the *viscerotropic* which involves the liver kidneys and heart and the *neurotropic* which attacks nerve tissue In nature the virus possesses both affinities and is said to be *pantropic* Strains which are predominantly neurotropic grow readily in tissue culture while viscerotropic strains require minced mouse embryo brain medium and chick embryo medium containing nerve tissue The virus can be maintained in the developing chick embryo and by inoculation into the testes of mice The various strains isolated in different parts of the world appear to be antigenically identical

History and Epidemiology Yellow fever occurs in large areas of South America and Africa Since 1948 an epidemic of sylvan yellow fever has been spreading northward through Central America and in the Caribbean area Much circumstantial evidence points to Africa as the place of origin of the disease but the first reported epidemic was in Yucatan in 1648 From that time until the twentieth century many outbreaks occurred in the coastal regions along the trade routes of the Atlantic The disease showed a seasonal incidence being common during the warmer weather and subsiding with the cold weather

Little was known of the method of transmission until Carlos Finley in 1881 incriminated the mosquito now known as *A aegypti* as the vector Because of the high incidence among American troops during the Spanish American War the Yellow Fever Commission was established under the direction of Major Walter Reed In 1900 and 1901 through experiments on volunteers in Cuba Reed Carroll Agramonte and Lazear proved the method of transmission by mosquitoes and showed that the causative agent could pass through a Berkefeld filter thus establishing the virus etiology of the disease Control and suppression of yellow fever followed mosquito eradication

The successful control of outbreaks which followed campaigns against *A aegypti* led to the formulation of the "key center" theory of epidemics by Carter From evidence that one attack of the infection produced a lifelong immunity Carter reasoned that two factors were necessary to keep yellow fever in a community (1) a population of nonimmune human beings and (2) a population of mosquitoes to act as vectors Epidemiologists surveyed the key centers and a tremendous control program was launched under the auspices of The Rockefeller Foundation with the optimistic belief that yellow fever could be eradicated from the Americas and eventually from the world The campaign appeared successful and the disease seemed to be disappearing from South America until a mysterious epidemic broke out in Rio de Janeiro in 1928

In this same year Stokes Bauer and Hudson working in West Africa demonstrated the susceptibility of rhesus monkeys to the virus In 1930 Theiler adapted the virus to white mice by intracerebral inoculations With the acquisition of susceptible experimental animals new tests were available for epidemiologic studies and the whole problem was reevaluated

The Rockefeller Foundation sponsored extensive surveys employing serologic tests and post mortem biopsy studies (viscerotomy service) which demonstrated conclusively that West Africa was not the last remaining key center but that the disease was far more widespread In the jungles and forests in large areas of South America Central America and Africa the disease is present in the monkey population and is transmitted by "forest loving" mosquitoes particularly species of *Haemagogus* This reservoir constitutes a potential source of danger to the native inhabitants and to rural workers who have to go into these areas With increasing air travel and closer communication with all parts of the world the danger of further widespread outbreaks is great particularly in Mexico and along the Gulf of Mexico Eradication of infection by antimosquito measures alone is no longer feasible

Pathogenesis and Pathology The mode of spread and multiplication of the virus has been studied in rhesus monkeys it presumably follows the same

ported in patients with this condition When dryness of the mucosal surfaces is a prominent feature the name *Sjogren s syndrome* is often applied although some insist that *Mikulicz s disease* (as opposed to the *syndrome* accompanying other diseases) is the proper term The chronicity of the process and its occurrence in elderly females makes confusion with mumps unlikely

The diseases that can produce aseptic meningitis are listed on p 1071

When orchitis occurs without parotitis unless mumps is epidemic the etiology is likely to be obscure Serologic testing may later establish the diagnosis of mumps Orchitis is a complication of pleurodynia leptospirosis relapsing fever and rarely of chickenpox In any patient with fever and orchitis brucellosis should be ruled out by appropriate tests (see p 901) Orchitis is a relatively rare complication of gonorrhea

Treatment There is no specific treatment for infections with mumps virus Patients with parotitis should receive mouth care analgesics and a bland diet Bed rest is advisable only as long as the patient is febrile contrary to popular belief physical activity has no influence upon the development of orchitis or other complications

Patients with epididymoorchitis are acutely ill and in great pain Many advocated forms of treatment including surgical decompression of the testicle estrogens convalescent serum and antibiotics have not been beneficial The administration of adrenal steroids in a dosage corresponding to 300 mg cortisone initially followed by a schedule of decreasing dosage for 6 to 7 days has been highly effective in the treatment of orchitis Pain swelling and fever subside dramatically within a few hours in most cases and such measures as suspensories and ice packs are usually unnecessary ACTH hydrocortisone and prednisone are all effective No adverse effect on the course of concomitant meningeal involvement has been noted

The management of pancreatitis is described on p 1477 Adrenal steroids in general have not appeared to alter the course of this complication in any dramatic fashion however in mumps arthritis these hormones have been found to give symptomatic relief

Prophylaxis After exposure to the virus has occurred the administration of gamma globulin is relatively ineffective in preventing or modifying mumps parotitis The use of a formalinized vaccine appears to reduce the incidence of symptomatic infection The disease in children is usually benign and vaccination after exposure is rarely justified However vaccination of exposed adults who show no reaction to skin test with mumps antigen is probably worthwhile

Diethylstilbestrol in a dosage of 1 mg daily for 1 week reduces the incidence of orchitis A preferable regimen is the administration of 20 ml gamma globulin prepared from mumps convalescent serum when parotitis appears

Prognosis Except for rare cases of fulminating encephalitis prognosis for life is good Deafness after meningoencephalitis or permanent diabetes after pancreatitis is rare

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measures usually employed For high fever and headache tepid sponges and ice caps are recommended

Prevention Prophylactic measures consist of vaccination and the eradication of *A aegypti* mosquitoes Two strains of attenuated yellow fever virus are available for the preparation of vaccines the French neurotropic and the 17D strain The yellow fever vaccine prepared from the 17D strain consists of macerated chick embryos which have been inoculated with the virus and allowed to harbor it for 4 days The chick embryo juice is desiccated and sealed in ampuls while in the frozen state For use the virus is reconstituted by the addition of sterile physiological saline solution Only one subcutaneous injection of 0 5 ml is necessary to produce immunity in man The 17D vaccine also produces immunity when introduced into the skin by scarification The French neurotropic vaccine is made of dried mouse brain infected with the French neurotropic strain of virus Vaccination consists of applying a gum arabic solution of the vaccine to the scarified skin Mass vaccination has been quite satisfactory In rural areas it is the only effective protection against jungle yellow fever

Before methods of vaccination were developed epidemics were controlled and eliminated whenever the *Aedes* mosquitoes and other vectors were eradicated Breeding of mosquitoes was controlled in and near dwellings by pouring oil into the containers where larvae were found The use of DDT spray on the walls of houses is now an effective preventive At present no method is available for eradicating jungle yellow fever

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183 PLEURODYNIA (Coxsackie B Disease)

Robert R Wagner

Definition This is an acute infectious disease caused by Coxsackie group B viruses and characterized by sudden onset of paroxysmal lower thoracic and abdominal pain and fever Common synonyms are *Bornholm disease epidemic myalgia* and *devil s grip*

Etiology Coxsackie viruses are primary intestinal parasites of man that resemble poliomyelitis viruses in size and in their resistance to heat and chemicals but differ in their characteristic pathogenecity for suckling mice and their affinity for striated muscle and fat There are many antigenic strains that are divided into two groups A and B on the basis of the histologic appearance of lesion in suckling mice Most group B and a few A strains can be grown in tissue culture and several also produce cardiac cerebral and hepatic lesions in infant mice and pancreatitis in infant or adult mice Group A Coxsackie viruses are the etiologic agents of herpangina (p 1091) but are otherwise relatively unimportant as human pathogens Group B viruses cause pleurodynia certain cases of aseptic meningitis and nonspecific febrile illnesses

Epidemiology Pleurodynia is a disease of the summer and autumn that occurs in epidemic form throughout the world All age groups are affected but the highest incidence is in children and young adults Explosive outbreaks with extremely high attack rates have been reported particularly in institutions but it is more usual for epidemics to start insidiously reach a peak in several weeks and subside over a period of months Multiple cases in a single household are infrequent indicative of a predominance of asymptomatic infections and carriers Infection is spread by close personal contact probably by the fecal oral route through fomites food and water Other modes of transmission are suggested by isolation of Coxsackie viruses from respiratory secretions sewage and flies

Pathogenesis The virus presumably invades the body from the intestinal tract and has been recovered from blood skeletal muscle cerebrospinal fluid spinal cord and myocardium Autopsies of the few fatal cases reported in infants have revealed extensive myocarditis focal degeneration and inflammation of brain and spinal cord and hemorrhagic lesions of the pleura Degeneration and focal inflammation have been noted in skeletal muscle obtained by biopsy

Manifestations The incubation period is usually 2 to 5 days but may be as long as 2 weeks Mild prodromal symptoms such as malaise sore throat coryza anorexia or myalgia may be present for

course in man although the virus has been isolated only once from a patient after death from yellow fever In monkeys it is primarily an infection of *the hematopoietic system and secondarily invades* other organs When inoculated intradermally the virus spreads immediately to the local lymph nodes where it multiplies After a few days it enters the blood stream and invades the liver spleen kidneys bone marrow and lymph nodes where it can be demonstrated several days after the blood stream no longer contains it

The pathologic lesions can be explained on the basis of infection and multiplication of the virus The organs which show the chief signs of degeneration are the liver kidneys and heart Hemorrhages and jaundice are present in the skin and mucous membranes The liver is normal or slightly enlarged and appears yellow and fatty when sectioned The kidneys are swollen and tense and also have a yellow fatty appearance The heart shows few gross abnormalities but cloudy swelling and patchy fatty degeneration are demonstrable on section The stomach usually shows erosion and punctate hemorrhages in the mucosa of the pylorus

Microscopic changes are most apparent in the liver The liver cells show marked midzone necrosis with fatty degeneration In severe cases entire lobules may show necrosis The Kupffer cells are enlarged and granular and the sinusoids are engorged The architecture remains intact and normal cells may be found about the central vein and the periphery of the lobule There is complete absence of inflammatory reaction

The lesions in the kidney are most evident in the tubules chiefly the convoluted portion where cloudy and fatty degeneration is present In the spleen as in the liver inflammatory reaction is absent

Manifestations The *incubation period* is 3 to 6 days The onset is usually sudden and acute sometimes with a chill but it may be insidious During the first 2 days of illness the chief symptoms are fever headache and backache Temperature rises moderately on the first or second day *Active congestion* follows characterized by flushed face and injected conjunctivas and scleras Nausea and vomiting are common

As the fever reaches a peak the pulse slows Jaundice and evidence of hemorrhage occur on the fourth or fifth day of illness Jaundice even in severe cases is not intense Subcutaneous hemorrhages may occur as petechiae or patchy ecchymoses and gingival bleeding is common Hemorrhages may occur in the stomach and intestine giving rise to black vomit and melena After 3 or 4 days of illness the temperature may fall and a remission of symptoms take place for a short time to be followed by a recurrence of fever

Proteinuria occurs early in the disease and the volume of urine tends to decrease Recovery begins about the seventh day it is rapid and usually without complications

There is wide variation in the severity of the disease from mild or subclinical infections to fulminating fatal cases with hemorrhages and icterus The over all mortality is estimated at 5 per cent Most deaths occur on the sixth or seventh day The characteristic signs whether in mild or severe cases are the rise and remission of fever the slow pulse in relation to the temperature (Faget s sign) and leukopenia

Laboratory Findings Proteinuria is marked in severe cases but is often absent in mild infections A terminal anuria may occur The leukocyte count falls steadily from the onset of infection leukopenia being most marked on the fifth or sixth day There is a decrease in both polymorphonuclear leukocytes and lymphocytes *As reflected in liver function* tests the liver is the organ most extensively damaged by the virus

Three laboratory procedures are available to establish a positive diagnosis isolation of the virus serologic tests which demonstrate development of specific antibodies during an infection and histologic examination of biopsies of the liver Isolation of the virus is possible by intracerebral inoculation of mice with serum from patients up to the fifth day of the disease The inoculated mice develop signs of encephalitis and the agent isolated must then be identified This is usually done by neutralization tests with specific immune serum against yellow fever Serum from patients may show positive protection tests in mice Two specimens are necessary one obtained as soon as possible after onset and a second obtained during convalescence Since antibodies develop very rapidly both specimens of serum must be titrated for their neutralizing property If the antibody content of the serum is higher during convalescence this indicates that the infection is probably yellow fever If the antibody content is the same in both specimens the patient probably has had a previous infection of yellow fever

Liver sections may be obtained by biopsy or in fatal cases in countries where the disease is endemic by the viscerotome This is a simple instrument which permits removal of small specimens of liver after death In South American countries where jungle yellow fever occurs over a large area the study of liver sections of any fatal febrile case of less than 10 days duration is a very important function of the Yellow Fever Service

Treatment No specific treatment is available Bed rest good nursing care and supportive therapy consisting of soft diet adequate fluids and saline and glucose infusions are the general therapeutic

184 HERPANGINA (Coxsackie A Disease)

Robert R Wagner

Definition This is a benign infectious disease of children characterized by sudden onset fever sore throat, and oropharyngeal vesicles

Etiology and Epidemiology Herpangina is a disease of the summer months caused by Coxsackie A viruses (see p 1059)

Manifestations Children under four years of age are most susceptible but the disease also occurs in older children and young adults The incubation period is usually 4 days but varies from 2 to 9 days Prodromal symptoms are uncommon and the onset is usually abrupt with fever of 100 to 105 F Anorexia vomiting abdominal pain and occasionally diarrhea may be present The most common complaint in older children is sore throat often accompanied by dysphagia and salivation Other respiratory symptoms are conspicuously absent and headache and myalgia are uncommon The only noteworthy physical findings are diffuse pharyngeal injection without exudate and the presence of from 2 to 20 small vesicles on the anterior faucial pillars soft palate uvula, pharynx and rarely on the tongue mouth or tonsils The lesions are from 1 to 2 mm in size grayish white in appearance and surrounded by a bright red areola They gradually enlarge to 3 to 4 mm in size and rupture leaving clean superficial punched-out ulcers The cervical lymph nodes may be slightly enlarged and tender Typical vesicles containing virus have also been described on the vaginal labia Febrile diseases without oropharyngeal vesicles are frequent during outbreaks of herpangina and probably represent abortive Coxsackie A infections Diseases in children known as 3-day fever" and epidemic summer grippe and sore throat are also thought to be related to herpangina

Fever persists for 1 to 4 days and *recovery* is always uneventful No *treatment* is required other than mild local anesthetics such as butycaine trochees

Laboratory Findings The blood leukocyte count is moderately elevated in about one fourth of the cases Virus is usually present in the feces and pharynx and serum antibodies develop during convalescence However the multiplicity of strains of Coxsackie A viruses and corresponding antibodies and their prevalence throughout the normal population make laboratory diagnosis difficult costly and time consuming

Differential Diagnosis Primary herpetic stomatitis caused by herpes simplex virus (p 1092) may also involve the oropharynx but unlike herpangina it does not occur in epidemics and lesions are more common on the gums and anterior part of the mouth The enanthems of measles and chickenpox aphthous stomatitis and bacterial pharyngitis may be confused with herpangina at first but are readily differentiated by their subsequent course (see p 852)

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185 HERPES SIMPLEX

Lewis L Coriell

Definition Herpes simplex is an infectious disease caused by a virus Classically it appears in recurrent attacks as clusters of grouped vesicles on an erythematous base having a predilection for the face lips and mucocutaneous junctions The initial infection in some individuals may be more serious or even fatal Infection of the central nervous system the eye the skin in eczematous patients the viscera or the mouth and throat in gingivostomatitis are the common forms of "primary herpes simplex

History Gruter in 1914 first transferred infection from the cornea of a patient to the cornea of a rabbit and subsequently back to the cornea of a blind man reproducing a typical dendritic ulceration of the cornea In 1938 Dodd Buddingh and Johnson isolated herpes simplex virus from the mouths of children suffering with febrile ulcerative stomatitis (acute herpetic gingivostomatitis) Burnet (1939) found no neutralizing antibodies in the acute serum from similar patients and antibodies developed during convalescence In 1941 a serious complication of eczema Kaposi s varicelliform eruption was shown to be caused in some cases by secondary infection of the abnormal skin with the virus of herpes simplex (eczema herpeticum)

Etiology The virus of herpes simplex passes ordinary bacterial filters quite readily and measures 125 to 150 mμ in diameter It is present in early vesicles It may be propagated on the cornea or in the brain of several laboratory animals on the

several days However the most characteristic feature of the disease is the sudden onset of severe sharp paroxysmal pain over the lower ribs or in the substernal area It is accentuated by moving breathing coughing sneezing or hiccuping and may be referred to the shoulders neck or scapulae Pain and spasm of the anterior abdominal muscles occur in about half the cases often in combination with chest pain but sometimes localized entirely to the lower abdomen Muscle tenderness is usually not prominent but some patients complain of intense cutaneous hyperesthesia and paresthesias over the affected area Headache is frequently present sometimes of excruciating severity and may be accompanied by delirium dizziness and true vertigo Fever of 100 to 105 F develops shortly after the onset of pain and is often preceded by chilliness or shaking chills The temperature may be elevated in the early morning fall to normal at midday and rise again in the evening Respiratory manifestations are not prominent but there may be mild pharyngeal injection and nonproductive cough Conjunctivitis and photophobia are rare A pleural friction rub is detectable in 10 to 25 per cent of patients and can persist after the pain subsides Transitory erythematous rashes have occasionally been noted Anorexia and nausea are frequent and vomiting and diarrhea often occur in children

Certain outbreaks of Coxsackie B viral infections have been characterized by a preponderance of nonspecific febrile illnesses without thoracic or abdominal pain Sore throat generalized lymphadenopathy splenomegaly and fever lasting for 2 to 14 days have been reported in children Another type of illness seen in adults is characterized by pain and tenderness of the neck occiput back shoulders or extremities The relationship of Coxsackie infections to epidemic fibrositis a disease with similar manifestations which occurs predominantly in the winter has not yet been determined

The complications of pleurodynia are largely the result of disseminated infection with the causative virus *Meningitis* can occur several days after the onset of pain and fever or it may be the sole manifestation of infection indistinguishable from other forms of benign aseptic meningitis Coxsackie meningitis occurs more frequently in children than in adults and is often a biphasic illness The incidence of *pericarditis* is unknown but *myocarditis* has been described in infants in association with *encephalitis* *Orchitis* developing in the second week of the disease has been a frequent complication in certain outbreaks but is rare in others Arthritis and jaundice have also been reported Otitis media and herpes febrilis are uncommon complications The average duration of illness is 4 days but varies from 1 day to several weeks *Relapses* occur in 25 to 50 per cent of cases usually 2 to 3 days after subsidence of the initial episode but sometimes after an interval of several months Some patients experience multiple attacks of equal severity Complete recovery may be delayed for weeks by generalized weakness but convalescence is otherwise uneventful and there are no known sequelae Deaths directly attributable to the infection have been reported only in infants with myocarditis Immunity is type specific and reinfection can occur with other types of Coxsackie virus

Laboratory Findings Isolation of Coxsackie B virus from the feces or throat washings does not constitute valid proof of infection unless supported by epidemiologic evidence Definitive diagnosis can be made only by demonstrating a rising titer of neutralizing or complement fixing antibodies in the serum This is a formidable and often unrewarding procedure because of the many strains of virus and the high incidence of asymptomatic infection X ray of the chest is normal except for rare instances of pneumonitis or pleural effusion The blood leukocyte count is usually normal but can be low or moderately elevated Slight eosinophilia sometimes occurs several days after onset or in convalescence The cerebrospinal fluid may be normal or may contain as many as 300 cells most of them mononuclear

Differential Diagnosis Pleurodynia is often confused with early bacterial pneumonia when pain is localized to the chest and with intra-abdominal disease particularly acute appendicitis when abdominal pain predominates In the absence of characteristic pain Coxsackie meningitis can be differentiated from other benign aseptic meningitides only by appropriate laboratory studies

Treatment Coxsackie viruses are not affected by antibiotics Aspirin codeine or morphine is often required for symptomatic relief of pain The usual measures for relief of pleurisy (p 38) may be helpful

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tum) is a rarer manifestation of primary infection which occurs in persons with eczema or neurodermatitis Large areas of abnormal skin are involved the grouped vesicles usually appearing in crops over a period of several days hence the similarity to varicella The fever may reach 106 F and marked prostration is not uncommon The fever subsides during the second week coincident with the crusting and healing of the skin lesions

Meningoencephalitis was formerly thought to be a rare form of primary herpes in man but complement fixation tests indicate that 5 to 7 per cent of cases of aseptic meningitis may be due to this virus It is accompanied by fever headache gastrointestinal symptoms and signs of meningeal irritation and encephalitis

In addition to the *syndromes* described above herpes simplex has been known to occur in segmental nerve distribution simulating herpes zoster The occurrence of repeated attacks in the same area is suggestive

Visceral disease characterized by fulminating generalized infection with fever viremia and necrotic lesions in the liver and other viscera and frequently terminating in death has been recently recognized as a clinical entity in newborn infants Skin lesions are not present in all infants Most cases have been in premature infants or when the mother was undergoing a primary herpetic infection herself In several cases the mother was known to have had repeated herpes vulvovaginitis and presumably the infant was infected in traversing the birth canal

Laboratory Findings The total leukocyte count is usually normal or only slightly increased with a normal differential index The diagnosis can be confirmed in the laboratory by (1) isolation and identification of the virus (2) demonstration of typical eosinophilic intranuclear inclusions in tissue sections or vesicle fluid or (3) in primary infections a rising titer of specific neutralizing antibodies The acute phase serum should be collected before the fifth day of illness as antibodies appear early In central nervous system infection the spinal fluid pressure and protein are slightly increased and a pleocytosis up to 500 cells is observed with many polymorphonuclear leukocytes early changing later to mononuclears

Differential Diagnosis The history and clinical appearance of the recurrent skin and eye manifestations are usually sufficient to establish the diagnosis

The laboratory tests enumerated above are confirmatory in doubtful cases and are essential for absolute diagnosis in the primary manifestations The condition is often confused with Vincent's angina or trench mouth which responds dramatically to parenteral penicillin Recurrent solitary aphthous ulcers in the mouth are not caused by herpes simplex

In herpangina caused by group A Coxsackie virus the vesicles are confined to the posterior part of the mouth and the disease occurs in epidemics Large bullae recurrent attacks and normal lymph nodes are seen in erythema multiforme

Eczema herpeticum may be easily confused with secondary bacterial infection of eczema Extensive weeping and crusting may obscure the grouped vesicular nature of the lesion before the crusts are removed by wet dressings Eczema vaccinatum (generalized vaccinia) usually presents larger vesicles with a central indentation but this characteristic is not constant Herpetic meningoencephalitis must be differentiated from bacterial and viral encephalitides particularly epidemic viral encephalitis poliomyelitis lymphocytic choriomeningitis and postinfectious encephalitis (see p 1071)

Treatment No specific treatment is available Repeated vaccination with calf lymph vaccinia virus is currently in vogue but the apparent successes can probably be explained by the supportive psychotherapy Laboratory studies reveal no cross protection or interference between these two viruses It is desirable to have the local treatment of eye lesions supervised by an ophthalmologist

Penicillin and other antibiotics may be helpful in controlling secondary bacterial infection In acute gingivostomatitis the maintenance of adequate hydration and nutrition are aided by the local application before meals of 1 per cent Pontocaine A detergent mouth wash such as 1 1 000 Zephiran helps to maintain oral hygiene and inhibit bacterial proliferation In eczema herpeticum and visceral disease supportive therapy fluid replacement blood transfusions and appropriate antibacterial measures are indicated Convalescent serum and gamma globulin have not been beneficial

Prognosis Except for complications following infection of the cornea recurrent herpes has high nuisance value but few sequelae The primary manifestations run a self limited course except for meningoencephalitis and visceral disease which are sometimes fatal and eczema herpeticum in which the mortality rate may be 20 per cent

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Epidemiology The serums of most adults (70 to 90 per cent) contain neutralizing antibodies against herpes simplex many of these individuals experience recurrent manifestations of disease under suitable stimuli Fever whether due to infectious diseases or artificially induced (fever blister) and the common cold (cold sore") are probably the most frequent precipitants of recurrent herpes while emotional disturbance physical fatigue sunburn menstruation and food allergy are less common The virus remains latent in the tissues between attacks but is sufficiently active to stimulate antibody production Virus has frequently been found in the saliva when there was no clinical evidence of disease Adults who have never been infected may contract a primary infection if suitably exposed Full term newborn infants are immune by virtue of transplacental transfer of antibodies which they gradually lose after the first few months of life However by the fifth year the percentage of children with specific neutralizing antibodies approaches that observed in adults indicating a high infection rate during infancy The clinical syndromes recognized as primary infection in this age group account for only 15 per cent of serologic infections Herpes simplex has evolved an unusually successful host parasite relationship with man Most people harbor the virus from infancy to old age with little inconvenience to themselves and even the primary contact in infancy is usually not accompanied by manifest clinical disease

Pathogenesis It is probable that during latent periods the virus lives within the cells since the body fluids contain sufficient neutralizing antibody to inactivate the virus The various precipitating factors which induce recurrent disease may have a common denominator in altered physiology of the host cell which permits the virus to multiply but little specific information is available on this point Skin biopsies taken during the early vesicular stage show congestion of the dermis with swelling and ballooning degeneration of prickle cells of the epidermis In some of these the nuclear basichromatin is collected at the periphery and the entire central area of the enlarged nucleus is filled with a homogeneous mass which at first stains blue and later red with hematoxylin and eosin This is the type A inclusion body found wherever there is active herpes simplex infection Multinucleated giant cells with each nucleus containing an inclusion body are frequently seen in biopsies of infected human skin

The intraepidermal vesicle does not extend below the basement membrane and hence does not cause scarring although depigmentation may persist for some time in dark skinned people In the healing phase the vesicle and corium are densely infiltrated with inflammatory cells

Manifestations *Recurrent herpes simplex* is a circumscribed eruption consisting of closely grouped thin walled vesicles on an erythematous base which tends to recur repeatedly in the same area of the skin particularly at mucocutaneous junctions It begins as a mild itching or burning lesions appear which rapidly become papular and vesiculate and then pass successively through crusting scab formation and desiccation the whole process taking from 3 to 14 days It is typically not accompanied by fever regional lymphadenopathy or other signs of systemic illness The disease is self limited and is commonly identified with its anatomic location—herpes facialis labialis nasalis progenitalis or vulvovaginalis

Herpetic keratoconjunctivitis is characterized usually by swelling and congestion of the conjunctiva with superficial opacities in the cornea and a palpable preauricular lymph node Bacterial cultures are sterile hypesthesia is a prominent sign The presence of typical herpetic vesicles on the eyelids may aid in the diagnosis however the recurrent attacks are frequently confined to the cornea in the form of dendritic ulcers or less often as punctate marginate or disciform ulcers The corneal ulcerations may persist for several weeks and respond poorly to local therapy they are superficial but the occurrence of repeated attacks poses a threat to vision

Traumatic herpes designates those cases where the primary infection occurs at the site of a skin abrasion on the hand elbow finger or other skin area not commonly associated with the disease Repeated recurrences have been observed at the same site over a period of many years

Acute herpetic gingivostomatitis is the commonest form of primary infection and is seen most frequently in children from one to four years of age less often in adults It is characterized by gradual or sudden onset with fever malaise sore mouth and throat and extreme irritability sometimes alternating with lethargy The fever may reach 104 F but is usually 101 to 103 F Physical examination reveals multiple painful shallow aphthous ulcers on a red base scattered over the buccal mucous membranes tongue and oropharynx The gums are swollen bleed easily on manipulation and are typically most inflamed at the gingival margin The regional lymph nodes are large and tender Fever and pain usually persist for 6 to 8 days followed by gradual healing of the ulcers during the following week The ulcers may be confined to or appear first in the pharynx (herpetic pharyngitis) and in such cases the diagnosis is commonly missed

Eczema herpeticum (Kaposi s varicelliform erup

187 DENGUE
Robert R Wagner

Definition Dengue is an acute viral disease characterized by a diphasic course fever myalgia morbilliform rash transient personality changes and leukopenia

Epidemiology The infection is transmitted by *Aedes aegypti* and other species of *Aedes* mosquitoes which harbor the virus throughout their lives but do not pass it on to their offspring Man and monkeys constitute the only known reservoirs of infection Dengue is endemic in tropical and subtropical areas where mosquitoes survive throughout the year Summer epidemics have occurred in the United States particularly in port cities but the climate of this country is not favorable for the establishment of endemic foci The epidemiologic characteristics of dengue closely resemble those of yellow fever the two diseases also have a similar geographic distribution except in southeast Asia where dengue is prevalent but yellow fever is unknown

Etiology Large quantities of virus are present in the blood during the early phase of the disease but nothing is known of the pathogenesis or site of viral multiplication Virus isolated directly from man or mosquitoes is infectious for volunteers but is not pathogenic for laboratory animals and produces no inclusion bodies or other recognizable lesions During the Second World War Sabin and Schlesinger demonstrated that dengue virus produces fatal encephalitis in suckling and adult mice after repeated brain passages Mouse adapted virus has been cultivated in tissue cultures of monkey kidney epithelium All strains of dengue virus fall into two immunologic categories designated as Hawaiian (type 1) and New Guinea C (type 2) Both types are related antigenically to the viruses of yellow fever and Japanese B West Nile and St Louis encephalitis

Manifestations The incubation period is usually 5 to 9 days with a range of 3 to 15 days About half the cases have a sudden and dramatic onset with chills or chilly sensations profuse diaphoresis and temperature elevation of 102 to 106 F Prodromal symptoms of malaise anorexia and lethargy precede the fever in milder forms of the disease Severe frontal headache retroorbital pain and excruciating low backache are almost invariably present Dengue is popularly known as breakbone fever" because of incapacitating pains in the muscles and periarticular tissues of the extremities in more than half the cases The majority of patients experience nausea constipation and disturbances of taste and smell in the early phases diarrhea may be present late in the course Agitation and insomnia alternate with depression and fitful sleep A primary rash consisting of blotchy erythema or flushing of the face accompanies the initial temperature elevation in about a third of the patients Moderate conjunctival and pharyngeal reddening may also be noted The symptoms persist for 3 or 4 days following which the temperature falls by crisis or rapid lysis A bright red morbilliform or punctate rash appears in three fourths of the patients on the third to sixth day of illness the eruption starts on the dorsal surfaces of the hands and feet and rapidly extends over the trunk and face Generalized lymph node enlargement is commonly encountered but the spleen is rarely palpable

Many patients develop a *secondary rise in temperature* 12 to 72 hr after subsidence of the initial episode producing the typical saddleback fever curve of dengue All the symptoms return with increased intensity delirium and depression may be particularly marked Cold mottled extremities hypotension bradycardia and a dicrotic pulse may be noted during the second phase of the disease The total duration of acute illness is usually 6 to 9 days but convalescence is often prolonged for several weeks by marked weakness apathy radicular pains aching legs and back and marked personality changes A rare disturbance is transient loss of pupillary accommodation owing to paralysis of the ciliary muscle of the eye

The incidence of *complications* varies in different epidemics Bleeding tendencies are occasionally noted as manifested by purpura petechial rashes epistaxes and hemorrhages from the intestine and vagina Jaundice occurs in less than 1 case in 100 Herpes labialis otitis media and bronchopneumonia are uncommon complications The mortality rate is consistently low

Laboratory Findings Complement fixing and neutralizing antibodies appear in the serum after the seventh day of disease Leukopenia of 2 000 to 5 000 cells per cubic millimeter and toxic granulation of the polymorphonuclear leukocytes are constant features of the early phase of the disease Moderate leukocytosis often occurs during convalescence Oliguria and proteinuria are common with high fever

Differential Diagnosis The sudden onset of chilliness fever and myalgia may simulate influenza malaria sandfly fever and leptospirosis but rash is uncommon in these diseases Exanthematous viral infections such as measles can usually be differentiated by their clinical course and epidemiology

Treatment No specific treatment is available but analgesics and sedatives afford symptomatic relief of pain and anxiety Control of mosquitoes by sanitation and insecticides decreases the incidence of dengue in endemic areas Dengue virus cultivated in mouse brain has been used as a living attenuated vaccine unfortunately it causes mild dengue

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186 PHLEBOTOMUS FEVER
W Elizabeth Gambrell

Definition Phlebotomus fever often referred to as *sandfly pappataci* or *3 day fever* is a benign self limited viral infection characterized by fever severe headache conjunctivitis general malaise and leukopenia It is transmitted by the sandfly *Phlebotomus papatasii*

Etiology The virus has been isolated by passing infectious human serum through gradocol membranes Its size is estimated at between 40 and 60 mμ In frozen or lyophilized states the virus has been preserved for many years In 1952 one strain of the virus from serum stored in the frozen state for 9 years was adapted to brains of newborn mice Several strains have been isolated and appear to be immunologically different as evidenced by lack of cross immunity in inoculated volunteers

Epidemiology The disease is endemic in tropical and subtropical countries particularly in those parts of Europe Africa and Asia between 20 and 45 north latitude where the vector *P papatasii* propagates In native populations it occurs during infancy and childhood as a mild febrile illness and is usually not recognized as a distinct clinical entity Outbreaks among military personnel and other immigrants who move into endemic areas occur with disturbing severity Patients are infectious for the sandfly 1 day before the onset of fever and 2 days after the onset The reservoir of the virus during the winter is not known

Manifestations After an incubation period of from 2 to 6 days there is sudden onset of malaise giddiness pains in the back and extremities severe headache (usually frontal) and pain in the eyes Fever is always present and lasts from 2 to 4 days The temperature may rise to 104 5 F usually within the first 24 hr then gradually subsides The pulse rate is fast at first but returns to normal more rapidly than the temperature and a bradycardia often occurs during convalescence An erythema occurs on the face and exposed parts of the neck and chest but no true rash develops The conjunctivas are injected and the eyeballs are tender Convalescence is characterized by prostration and occasionally by marked mental depression

Laboratory Findings A leukopenia with a predominance of neutrophilic leukocytes many of which are immature is present and there is a decrease in lymphocytes The greatest drop in the leukocyte count occurs at the end of the febrile period The urine is normal and there is no laboratory evidence of liver damage

Differential Diagnosis The diagnosis usually is made on clinical and epidemiologic grounds and is suggested by the occurrence of fever of short duration during the hot dry season in countries known to harbor the vector Phlebotomus fever is sometimes confused with dengue influenza infectious hepatitis and malaria It differs from dengue in the short duration of the fever and the absence of rash and lymphadenopathy from influenza by its seasonal incidence and the absence of catarrhal symptoms from infectious hepatitis by the absence of jaundice and by normal liver function tests Cases are often misdiagnosed as malaria but no chills occur and blood films are negative for parasites

Treatment No specific therapy is known Control measures consist of eradicating the vector within 100 to 200 m of living quarters DDT residual spray is successful in killing *P papatasii* at its breeding site and within habitations

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been observed Generalized skin eruptions and arthritis have also been described these apparently have been provoked occasionally by the performance of skin tests for the disease

Many years after the onset of the infection the patient may develop a proctitis associated with rectal bleeding and a purulent discharge Eventually there is scar formation and a complete fibrous ring may develop producing a *rectal stricture* which may necessitate colostomy Rectal lesions are found predominantly in women and are the result of the lymphatic drainage from the posterior part of the vulva and the vagina into the perirectal and retroperitoneal lymph nodes In the male the lymph vessels drain from the penis to the inguinal area and thence to the deep iliac nodes Rectal involvement in the male is often due to direct infection of the anorectal area

Another late complication of lymphogranuloma venereum is elephantiasis of the external genitalia This is known as *esthiomene* and is caused by interference with lymphatic drainage Ulceration is frequent and secondary infection may cause marked destruction of the genitalia

Diagnosis Isolation of the virus is the most accurate means of diagnosis but it is too laborious for general use The diagnosis is usually based upon the clinical findings together with a positive intradermal test and complement fixation reaction Commercial antigens are available for these A positive skin (Frei) test is of limited value as it merely indicates that the patient has been infected with the virus at some previous time In a recently acquired infection the complement fixation test will usually be positive in a high titer (1 80 to 1 640) Furthermore a change in the titer of circulating antibodies may be found in successive tests Biopsy of the primary lesion or of a lymph node should be done whenever feasible since the histologic picture is sufficiently characteristic to permit a diagnosis and to differentiate this disease from other venereal infections

Treatment Sulfonamide therapy has been the standard treatment of the early manifestations of lymphogranuloma venereum Sulfadiazine in doses of 4 Gm a day usually results in disappearance of symptoms and lesions within 1 to 2 weeks Chloramphenicol and the tetracyclines have been found to be of some value in the treatment of buboes draining sinuses and early proctitis These antibiotics do not seem to be more effective than the sulfonamides There is evidence to suggest that sulfonamide therapy may not destroy the virus completely and that it may persist in the body after the acute infection has subsided The late manifestations of the disease such as rectal stricture and elephantiasis do not usually respond to any form of medication and treatment is chiefly surgical Buboes which have become fluctuant should be aspirated to prevent spontaneous rupture and subsequent sinus formation

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189 COLORADO TICK FEVER

Edward S Miller

Definition Colorado tick fever is an acute infectious illness with a characteristic intermittent fever It is caused by a filtrable virus and transmitted to man by the bite of an infected tick

Etiology The causative agent is a small virus (35 to 50 mμ) It is unusually hardy and can be recovered from specimens of human blood which have been shipped unrefrigerated via ordinary mail routes The virus produces a fatal disease in suckling mice and hamsters it can be adapted to the adult mouse and to the chick embryo This is the only tick transmitted virus disease of man found in the Western Hemisphere

Epidemiology All cases so far reported have originated in the western part of the United States Colorado Wyoming Oregon Utah Idaho California Montana, Nevada and Washington Since many tourists visit these states during the tick season and since Colorado tick fever is a decidedly common affliction it is incumbent on North American physicians to be aware of this disease Affected persons usually give a history of having been in a tick infested area 3 to 6 days prior to the onset of symptoms In many instances patients can recall having found ticks on themselves however the

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188 LYMPHOGRANULOMA VENEREUM

Albert Heyman

Definition Lymphogranuloma venereum is a virus disease usually transmitted by sexual contact and characterized by a small primary lesion regional lymphadenitis and constitutional symptoms The disease is known by a variety of names such as *lymphogranuloma inguinale lymphopathia venereum* and *climatic bubo* but the name generally preferred is *lymphogranuloma venereum* This disease should not be confused with granuloma inguinale an ulcerative infection of the skin caused by the Donovan body (p 916)

Etiology The etiologic agent of lymphogranuloma venereum is a comparatively large virus When stained by special methods the organism can be seen with the ordinary microscope as small spherical granules or elementary bodies The virus is also distinctive in that it is susceptible to sulfonamide therapy It produces meningoencephalitis in mice and monkeys and can be cultured in the yolk sac of the chick embryo Infected yolk sac tissues are used as diagnostic antigens for intradermal (Frei) tests and complement fixation reactions There are serologic cross reactions however with psittacosis and certain other viruses (meningopneumonitis feline pneumonitis)

Incidence Lymphogranuloma venereum exists in almost every part of the world but is especially prevalent in tropical and subtropical countries It is frequently seen in the southeastern portion of the United States particularly among Negroes There is no accurate information regarding the incidence of the disease Only 880 new cases were reported in the United States in 1955 but it is likely that the incidence is much higher

Pathogenesis Lymphogranuloma venereum is nearly always transmitted by sexual contact The incubation period varies from 2 to 30 days A small evanescent lesion may appear at the site of inoculation but more often the first sign of the infection is inflammation and suppuration of the inguinal lymph nodes The virus is apparently disseminated throughout the body by way of the blood stream it has been isolated from the primary lesion the regional lymph nodes the blood and the spinal fluid Severe systemic manifestations such as meningoencephalitis keratitis cutaneous lesions and arthritis may occur Specific evidence of immunity to the virus including skin sensitivity of the tuberculin type and complement fixing humoral antibodies can be demonstrated in almost every patient shortly after the onset of the disease Positive skin and complement fixation reactions persist for several years Patients with lymphogranuloma venereum frequently have an increase in the globulin fraction of the blood Following the initial infection the patient may remain asymptomatic for a long period of time but may eventually develop late manifestations of the disease such as rectal strictures or elephantiasis of the genitalia

The early histologic lesion of lympogranuloma venereum consists of a granuloma forming about a small blood vessel and composed of large mononuclear cells The vessel is eventually compressed and obliterated and necrosis occurs in the center of the granuloma Polymorphonuclear leukocytes enter the area and an abscess develops The stellate abscesses which are thus formed are characteristic of the fully developed acute lesions of this disease

Clinical Manifestations The initial lesion of lymphogranuloma venereum is seldom noted since it is transitory and inconspicuous Those which are observed consist of single small shallow ulcerations on the external genitalia Shortly after the appearance of the initial lesion there are enlargement and suppuration of the regional lymph nodes The usual site is the inguinal or femoral region and this lymphadenitis is called the *bubo* The typical lymphogranuloma bubo develops slowly is bilateral and forms an ill defined lobulated mass Suppuration usually follows producing multilocular areas of fluctuation which may rupture spontaneously forming one or more draining fistulas

The majority of patients with buboes show constitutional reactions headache malaise fever and anorexia The systemic symptoms and buboes may subside spontaneously and may be the only clinical manifestations of the disease Occasionally the virus causes inflammation of distant areas and aseptic meningitis pericarditis and conjunctivitis have

Manifestations Systemic symptoms are usually mild consisting of headache fever and malaise which subside within a few days Shaking chills and fever as high as 104 F can occur but are unusual A transient macular or vesicular rash which subsides within 48 hr is rarely present during the early stages Erythema nodosum has been reported in one case

In a typical case the *primary* lesion consists of a raised slightly tender papule crowned by a small vesicle or eschar it often resembles an indolent furuncle or insect bite Multiple primary lesions have been described Some patients do not exhibit a lesion

Regional adenopathy becomes evident in from a few days to as long as 6 weeks after infection The axillary and epitrochlear femoral or (most commonly) the cervical nodes on one side become visibly swollen and tender often with redness of the overlying skin The nodes occasionally suppurate soften, and drain spontaneously fistulas always heal completely with only slight scarring Usually the tenderness subsides gradually and nontender firm enlarged nodes remain palpable for some weeks or even months There is no generalized glandular enlargement and the spleen is not palpable

It seems probable that clinical forms of this infectious disease other than that described above may be delineated A few cases of *encephalitis* associated with localized adenopathy and a positive skin test have been reported European authors have suggested that *nonspecific mesenteric lymphadenitis* in children is an abdominal form of cat scratch disease and in at least one reported case a previously negative skin test became positive after an illness diagnosed at laparotomy as mesenteric adenitis A number of cases of so-called *Parinaud's oculoglandular syndrome* characterized by conjunctivitis and regional lymphadenopathy and previously thought to be due to infection by *Leptothrix* have been reported to show positive skin tests for cat scratch disease Evidence for a primary *pulmonary* form is scant but suggestive Specific diagnosis is made by means of a skin test Antigen for this is prepared from pus aspirated from infected nodes it is inactivated by heating at 60 C for 2 hr A positive reaction is of the delayed tuberculin type appearing in 24 to 48 hr Patients in this country have reacted to antigens prepared from European countries and vice versa—evidence that the disease is widespread and that strain differences in skin test antigens are not significant Skin reactivity to the antigen persists for at least 4 years after the disease The Frei test is negative The leukocyte count is usually normal occasionally reaching 13 000 There may be some increase in eosinophils but this is not prominent The erythrocyte sedimentation rate is usually elevated In one reported case serum globulin was elevated early in the disease decreasing with convalescence (reminiscent of lymphogranuloma venereum) and in another a biologic false positive serologic test for syphilis was noted The histologic picture in excised nodes is that of a granuloma with microabscess formation although not diagnostic the pathologic findings are characteristic enough to suggest the possibility of the disease

Cat scratch disease is a benign illness and the prognosis is uniformly good Its main clinical importance lies in its possible confusion with other more serious diseases of the lymphatics Diseases to be considered are tularemia lymphatic tuberculosis sporotrichosis lymphogranuloma venereum and bacterial adenitis Because of the indolent character of the adenopathy Hodgkin s disease or other lymphomas may be suspected Appropriate serologic and cultural tests serve to rule out other infections biopsy may be needed to exclude tumor but a positive skin test with cat scratch antigen effectively rules out the necessity for such procedures

Treatment In instances of node suppuration aspiration of accumulated pus affords relief of pain (and incidentally serves as a source of material for the preparation of skin test antigen) Penicillin and streptomycin are ineffective Tetracycline drugs appear to shorten the course of the disease appreciably but their effect is usually not dramatic

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191 HEMORRHAGIC FEVER

J E Smadel

Definition Hemorrhagic fever is an acute illness characterized by fever of 5 days duration accompanied by prostration anorexia and vomiting Capillary abnormalities appear early in the illness they are intensified about the fourth day when petechial hemorrhages become prominent and increased capillary permeability results in marked proteinuria and transudation of plasma constituents into some soft tissues With the termination of fever some patients proceed to recovery but about 20 per cent develop hypotensive shock and renal insufficiency The mortality rate is about 5 per cent No specific laboratory test is available hence the

bites often pass unnoticed Cases occur most frequently in the spring and early summer when ticks are most prevalent The principal vector in the western United States is the wood tick *Dermacentor andersoni* the only tick in this area which commonly feeds on man In some heavily infected areas of the West as many as 14 per cent of ticks carry the virus

Manifestations The *incubation period* is 3 to 6 days Illness appears abruptly with chills or chilly feelings rapid rise in temperature to 102 to 104 F *unusually severe headache muscular aching photo*phobia malaise nausea and considerable prostration These symptoms continue for 1 to 3 days after which the temperature returns to normal and the patient feels nearly well After an interval of 1 to 3 days the fever returns and the same symptoms reappear though sometimes in a milder form This episode also lasts for 1 to 3 days and then the patient recovers Occasionally one sees single *or triple episodes of pyrexia but the typical tem*perature curve presents a distinctive saddleback configuration There are no abnormal physical findings in the usual cases other than those related to fever Convalescence is well established by the end of 7 to 10 days There have been indications that the disease is not always so benign as was formerly thought Several authenticated cases of encephalitis have been seen with abnormal neuro*logic signs and spinal fluid findings*

Laboratory Findings The white blood cell count is helpful in diagnosis as there is a leukopenia which is most marked during the second febrile period Total leukocyte counts of 2 000 to 3 000 per cubic millimeter are common The percentage of polymorphonuclear leukocytes is less than normal and there is a shift to the left Viremia is present throughout both febrile periods as well as *during the remission Complement fixing and neu*tralizing antibodies can be demonstrated in the serum for 10 to 30 days after onset of illness

Differential Diagnosis The disease was originally thought to be a mild variety of Rocky Mountain spotted fever and there is still considerable confusion because of the fact that both are tick borne and both occur in the Rocky Mountain region The initial manifestations of Colorado tick fever are not very distinctive in fact they are common to many viral and rickettsial infections such as influenza psittacosis viral encephalitis typhus and Rocky Mountain spotted fever The symptoms saddleback fever and leukopenia bear a striking *resemblance to dengue but the latter is accom*panied by an eruption and is found in a different geographic area

Treatment The known antibiotics are without value and there is no specific treatment Analgesics and sedatives are used for alleviation of symptoms

Prognosis No relapses are seen and no deaths have been reported Recovery is followed by prolonged *probably lifelong active immunity*

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190 CAT SCRATCH DISEASE

Ivan L Bennett Jr

Definition and Etiology Cat scratch disease is a specific infection characterized by indolent occasionally suppurative regional lymphadenitis secondary to a primary cutaneous lesion at the site of inoculation usually a minor trauma Because more than half of the reported cases have originated from *cat scratches and a history of close contact* with cats is often elicited the name *cat scratch disease* has become popular However the disorder has been acquired from splinters thorns beef bone fragments etc and in a fair percentage of patients no inciting trauma is recalled Other names such as *nonbacterial regional lymphadenitis* or *benign inoculation reticulosis* have been suggested but have not been widely used

A specific etiologic agent has not been identified Bacterial cultures of involved nodes are uniformly negative The disease has been transmitted by inoculation of pus from suppurating nodes into monkeys and man but numerous attempts to isolate a virus have failed Intranuclear and *intracyto*plasmic inclusions are seen in histologic preparations of infected nodes furthermore complement fixing antibodies for lymphogranuloma venereum antigen are occasionally demonstrated in sera of patients with this disease These suggest that a virus perhaps related to the lymphogranuloma psittacosis group may be the causative agent

Careful observation of cats thought to be re*sponsible for the disease has revealed no evidence* of illness these animals do not react to intradermal injection of antigen These facts together with the evidence that other forms of trauma transmit the disease may indicate that the infecting agent is *simply transmitted passively by the cat s claws*

fifth to seventh day after onset or progressive renal failure during the second week or both The acute renal failure is in no way unique in regard to its clinical manifestations hence this phase needs no further discussion here (see p 1367) The physical findings in the shock phase are those of peripheral vascular collapse In spite of the marked lowering of blood pressure the skin is warm and flushed The loss of plasma through damaged capillaries and pooling of blood in dilated peripheral and visceral capillaries result in reduced circulating blood volume All these abnormalities contribute to the profound dysfunction of selected organs such as the kidney

Laboratory Findings and Pathology Clinical laboratory data other than those already mentioned consist of (1) leukocytosis of 10 000 to 20 000 per cubic millimeter with many immature granulocytes by the end of the first week (2) thrombocytopenia which reaches levels below 100 000 in half the patients (3) disturbances of electrolyte balance and (4) entirely negative results in various types of tests for the ordinary microbial agents

The characteristic lesions observed at autopsy are found in the kidney right auricle and pituitary gland The renal cortex is pale while the pyramids are dark red almost hemorrhagic in appearance Hemorrhages occur in the auricle and pituitary gland If death ensues during the hypotensive phase gelatinous edema fluid is found in the retroperitoneal tissue and mesentery if death occurs during the late oliguric phase these tissues are usually dry Microscopic changes other than those concerned with the lesions observed grossly are rather meager and consist of scattered small focal areas of necrosis and hemorrhage in visceral organs Inflammatory lesions of the small vessels are conspicuously lacking but intense capillary congestion is characteristic Indeed many of the areas which appear hemorrhagic at autopsy such as the renal pyramids actually represent sites where the capillaries are extremely dilated

Differential Diagnosis During the first few days of illness the disease may be confused with leptospirosis the typhus fevers hemorrhagic smallpox idiopathic thrombocytopenic purpura leukemia or even influenza A history of exposure in the endemic area—particularly during a seasonal epidemic—and the appearance of marked proteinuria on the fourth day and the subsequent progression of the illness through the typical hypotensive oliguric and diuretic stages eliminate other diseases and warrant the diagnosis "hemorrhagic fever confirmed

Treatment and Prevention The treatment of hemorrhagic fever is limited at present to supportive measures none of the chemotherapeutic or antibiotic agents has proved of value Treatment begins with early diagnosis and prompt transfer to a hospital equipped to cope with a disease characterized by such extensive and varied physiologic disturbances

During the febrile phase complete bed rest mild sedation maintenance of reasonably normal water balance (overhydration is to be avoided) and an adequate but light diet are essential The majority of patients in the hypotensive and oliguric phases do well on a continuation of the same regimen but the severely ill require constant attention and often markedly different therapeutic measures within short periods of time Shock may develop rapidly and require prompt and active measures

Once diuresis is established special attention must be paid to adequate intake of fluid and electrolytes since 3 to 6 liters of urine may be excreted daily The principal therapeutic measure during convalescence is concerned with exercise the amount is increased *pari passu* with the recovery of concentrating capacity of the kidney

Preventive measures against hemorrhagic fever are based on avoidance of trombiculid mites which are assumed to be the vectors of the disease These measures are concerned with (1) the use of insect repellents for impregnation of clothes (benzyl benzoate) and application to exposed skin surfaces (dimethyl phthalate) (2) clearing of all vegetation from camp sites (bulldozing) and treatment of the area with residual insecticides such as lindane and (3) rodent control in and about camps by means of rodenticides

Prognosis The disease varies greatly in severity In some patients it is so mild as to make the diagnosis difficult indeed many suspected cases are not confirmed because they fail to develop the typical renal manifestations yet some of the patients with such cases undoubtedly are infected with the agent of hemorrhagic fever About 20 per cent of the diagnosed cases become critically ill The following factors contribute to the severity and influence the prognosis unfavorably delayed initiation of medical care prolonged high fever excessive fluid intake prolonged or recurrent shock persistent hemoconcentration anuria and progressive severe electrolyte disturbances The fatality rate in cases among American soldiers in Korea was between 5 and 7 per cent

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diagnosis is based on the typical clinical or pathologic picture Treatment consists of supportive and corrective measures

History Etiology, and Epidemiology One particular form of hemorrhagic fever occurs in northeast Asia along the tributaries of the Amur River where it was known to the Japanese in Manchuria and the Russians in Siberia about two decades ago and in Korea where it was recognized more recently The identical disease has been described in European Russia in the Yaroslavl area of the Volga River Basin The malady is similar to but distinct from a number of other hemorrhagic fevers which exist in several parts of the Union of Soviet Socialist Republics and in Scandinavia (see the review by Gajdusek under References at the end of the chapter)

Two seasonal peaks of disease incidence are characteristic of Far Eastern hemorrhagic fever but sporadic cases are encountered during each month of the year Most of the patients are seen between mid April and early July and between early October and early December More than a thousand cases occurred annually among United Nations troops in Korea from 1951 to 1953 Thereafter the incidence decreased rapidly and only a few cases were recognized in 1956 The disease in Korea was limited essentially to military personnel stationed in rural areas north of a line drawn across the peninsula at the level of Seoul However a few civilians of all ages contracted the illness on returning to neglected farms in this area after the armistice

The majority of cases were isolated and widely spaced in regard to time place and personnel but small outbreaks did appear in military units Intensive study of such outbreaks and other observations indicated that (1) there was no person to person spread of infection (2) food and water were unimportant in the epidemiology of the disease and (3) the cases in a given outbreak acquired their infection over a period of a day or so during exposure in a sharply localized area of abandoned farm land or scrub covered terrain All these observations point to an insect vector with limited mobility and with a capacity to infect man which is effective for only short periods of time and which is ineffective during the warm and the cold months of the year

Both the Russian and the Japanese investigators who studied hemorrhagic fever in the Amur valley were able to transmit the disease to human beings by injecting them with urine or blood taken from patients during the first few days of disease Moreover each group found that the causative agent passed through filters which retained microbiologic agents larger than viruses Neither these workers nor the Americans who investigated the Korean malady were able to establish the agent in a laboratory host Recent studies on this type of hemorrhagic fever in the Yaroslavl area have given identical results i e successful experimental transmission to man but not to laboratory animals

There are many similarities between the epidemiology of hemorrhagic fever and that of scrub typhus which is transmitted by trombiculid mites (p 1036) Moreover among the various terrestrial arthropods found in the endemic areas of Korea only trombiculid mites occur in abundance during both the spring and fall outbreaks of hemorrhagic fever and are scarce when human cases are infrequent Although definitive proof is lacking it is assumed that trombiculid mites serve as the vector for the agent of hemorrhagic fever and that small wild rodents provide the reservoir for the agent

Manifestations Following an incubation period of about 2 weeks (with extremes of from 9 to 36 days) the illness usually begins abruptly with frontal headache chills high fever anorexia and backache Physical findings during the first few days of fever and prostration are essentially limited to cutaneous flush especially about the face and neck and injection of the conjunctivas About the third day petechiae generally appear on the soft palate and in the conjunctivas the axillary folds and cutaneous areas subjected to mild trauma Increased capillary permeability becomes evident about the fourth day with the appearance of pathognomonic severe proteinuria and edema of loose tissue edema of conjunctivas and periorbital tissue is visible on physical examination Edema in the lumbar gutters and mesentery contributes to the abdominal and back pain but it can be seen only at autopsy

Fever disappears about the fifth day but even in the moderately affected patient the disease continues progressing through a series of phases i e hypotensive oliguric diuretic and convalescent Manifestations of capillary leakage among them a rising hematocrit increase during the hypotensive phase but begin to abate after several days when the oliguric phase is ushered in with its associated mounting blood urea and creatinine levels With the beginning of diuresis on about the tenth day symptoms and abnormal physiologic findings generally disappear quickly However renal tubular function is restored slowly and normal concentrating capacity usually does not return until the fourth to sixth week after onset of the disease Body weight which may have decreased as much as 20 lb in the average individual during the acute illness is slowly restored to pre onset levels

Those patients in whom the disease takes a severe course display either hypotensive shock during the

is highly effective Inclusion conjunctivitis of the newborn should not be confused with gonococcal ophthalmia which invariably begins 24 to 72 hr after birth

EPIDEMIC KERATOCONJUNCTIVITIS
(Shipyard Conjunctivitis)

This is an acute infectious disease of the conjunctiva and cornea An etiologic agent has recently been identified by Jawetz and coworkers as a member of the adenovirus group type 8 (see p 1041) Epidemic keratoconjunctivitis in the United States occurs mainly in localized outbreaks in factories shipyards and eye clinics The mode of transmission is unknown but the incidence of secondary cases in family contacts is low The incubation period varies from 5 to 10 days The disease begins unilaterally with mild or severe conjunctivitis that tends to be follicular in type and is sometimes associated with pseudomembrane formation iritis and subconjunctival hemorrhages Transient fever headache and malaise are the only systemic manifestations The preauricular lymph node is usually enlarged on the affected side Within a few days the cornea becomes inflamed with resultant pain lacrimation photophobia and blurred vision The other eye is involved several days after the first in about half the cases Subepithelial corneal opacities without ulceration appear 1 to 3 weeks after onset and can persist for years resulting in impairment of visual acuity Specific chemotherapy is not available but local hydrocortisone may suppress the inflammatory reaction Epidemics can be limited by restricting contact with known cases Infections that must be differentiated from epidemic keratoconjunctivitis include Newcastle disease herpes simplex (p 1091) leptospirosis (p 1017) and cat scratch disease (p 1098)

NEWCASTLE DISEASE

This is a common and economically important disease of poultry caused by a virus of the myxovirus (influenza) group The infection in birds may be acute or chronic and is characterized by severe manifestations of respiratory gastrointestinal, and central nervous system involvement. Human infection occurs mainly in poultry workers and virologists In man accidental introduction of contaminated material into the eye is followed in 24 to 72 hr by conjunctivitis edema of the lids and profuse lacrimation The cornea is not involved and photophobia is uncommon Constitutional symptoms are absent or mild The preauricular lymph node on the affected side is swollen and tender in about half the cases Recovery is complete in 10 to 14 days and no permanent damage results The diagnosis can be suspected from the patient s occupation and confirmed by isolation of the virus in embryonated eggs The antibody response to conjunctival infection is weak and serologic tests are generally unsatisfactory No treatment is available or required

WARTS (Verrucae)

Warts are specific infectious lesions of the skin and mucous membranes caused by a virus or group of viruses The disease has been transmitted to volunteers by cutaneous inoculation of ground suspensions of warts Virus particles and inclusion bodies can be seen in histologic sections examined under the electron microscope The disease is only mildly contagious but minor epidemics have been reported Individual susceptibility seems to vary considerably with age and trauma The lesions are classified clinically by their appearance and location *Flat warts* are small round lesions usually found on the back of the hands and on the face of children *Filiform warts* occur mostly on the face and lips of adults and have numerous small fingerlike projections The *common wart* (*verruca vulgaris*) usually appears on the hands or under the fingernails as multiple raised papules with rough horny surfaces *Plantar* and *palmar warts* are deep painful flat lesions of the soles and palms covered by a thick layer of cornified epithelium *Condylomata acuminata* (moist warts) occur on the external genitalia and perineal region of young adult women and men after sexual intercourse or other contact They appear as multiple grapelike clusters that are easily differentiated from the flat condylomata lata of secondary syphilis

All forms tend to recur after removal Various methods of eradication have been employed including surgery electrodesiccation x ray freezing with solid carbon dioxide and application of caustic chemicals such as phenol, salicylic acid or silver nitrate Local application of podophyllum resin has been effective for condylomata acuminata

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is a benign infectious disease of the skin caused by a virus of the pox group The natural mode of transmission is unknown but the disease has been produced in man by cutaneous inoculation of molluscum particles Individual lesions begin as tiny papules which gradually enlarge over a period of months to a size of 1 cm or greater The fully formed lesion is a round pink waxy nodule with a centrally depressed crown. Older lesions becomes pedunculated and

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192 VIRAL INFECTIONS OF THE EYE, SKIN, AND MUCOUS MEMBRANES

Robert R Wagner

The diseases described in this chapter are caused by viruses which characteristically produce localized infections in human beings They are transmitted by *direct contact or fomites* and have a low degree of contagiousness for man Although these infections are mainly of concern to ophthalmologists and dermatologists they sometimes enter into the differential diagnosis of systemic disorders that can involve the eye skin or mucous membranes A history of exposure and awareness of variations in host susceptibility will aid in their recognition Occupational contact with animals or animal products is the prime consideration in the diagnosis of Newcastle disease orf milker's nodules foot and mouth disease and vesicular stomatitis The prevalence of trachoma is largely related to poverty and overcrowding whereas epidemic keratoconjunctivitis occurs in localized outbreaks among factory and shipyard workers Age is the primary factor in susceptibility to inclusion *conjunctivitis* the several types of warts and molluscum contagiosum

TRACHOMA

Trachoma is an infection of the eye caused by a large virus related to the agents of lymphogranuloma venereum and psittacosis *Experimental* infections have been produced only in man apes and monkeys The disease is probably transmitted by fingers fomites and flies and is endemic in areas with poor sanitary conditions and low standards of living After an incubation period of *from 5 to 7* days trachoma begins insidiously or acutely with follicular conjunctivitis abundant purulent discharge swelling of the lids and enlargement of the lachrymal glands and preauricular lymph nodes This acute stage may last for several weeks before giving way to a subacute phase characterized by marked edema of the lids the formation of conjunctival blebs and progressive corneal involvement In the final stage of the disease scarring and contractures occur the lids frequently become everted and the cornea is invaded by dense fibrous tissue and blood vessels (pannus) Recurrent irritation ulceration and secondary bacterial infection commonly lead to blindness The diagnosis is most easily established in the acute stage of the disease by demonstrating typical inclusion bodies in smears of conjunctival scrapings stained with iodine or Giemsa stains Acute trachoma can be successfully treated with oral and local tetracyclines or chloramphenicol Surgery is required for removal of scar tissue in the advanced stages of the disease

INCLUSION CONJUNCTIVITIS
(Inclusion Blennorrhea)

This is an acute infectious eye disease of newborn infants children and adults It is caused by a virus similar to that of trachoma which resides in the genitourinary tract and is transmitted by sexual *intercourse* Genitourinary infection is usually asymptomatic but mild cervicitis and urethritis can occur The eyes of newborn infants are infected during passage through the birth canal ocular infection can also be contracted in swimming pools and nurseries The disease in infants is characterized by follicular conjunctivitis profuse mucopurulent exudate and pseudomembrane formation 5 to 9 days after birth The acute illness usually runs its course in several weeks but low grade conjunctivitis sometimes persists for many months Scarring and pannus formation do not occur Inclusion conjunctivitis in adults is an invariably mild afebrile infection usually confined to the palpebral conjunctiva of the lower lid Smears of conjunctival scrapings reveal inclusion bodies identical with *those of trachoma the two diseases* can be differentiated only by the clinical picture and course Oral or local treatment with tetracycline compounds

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193 ENTERIC VIRUSES

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Acute gastrointestinal disorders are second only to respiratory diseases as causes of disability Bacterial and protozoan infections account for a relatively small proportion of the total number of cases of gastroenteritis in the United States Most of the remainder are thought to be of viral etiology It is now known that a variety of viruses commonly inhabit the intestinal tract of man Poliomyelitis (p 1068) and Coxsackie A and B viruses (pp 1089 1091) are frequently present in feces of healthy individuals systemic diseases are relatively rare consequences of infection with these organisms The tissue culture techniques devised for detecting poliomyelitis viruses have resulted in the isolation of a great number of intestinal saprophytes known collectively as orphans" or ECHO (enteric cytopathogenic human orphan) viruses Types 6 and 9 ECHO viruses have been implicated as causes of benign aseptic meningitis but in general these organisms appear to live symbiotically in the intestinal tract and are rarely pathogenic It is likely that similar host parasite relationships exist for the viruses of infectious hepatitis (p 1486) Boston exanthem (p 1063) and erythema infectiosum (p 1063) but the incidence of asymptomatic carriers of these agents is not known The frequency with which the known enteric viruses produce symptoms of gastroenteritis without systemic illness has not yet been determined However during epidemics of poliomyelitis Coxsackie infections and infectious hepatitis diarrhea can be the sole manifestation of infection particularly in young children There is evidence that ECHO viruses may be responsible for outbreaks of acute febrile diarrhea in children and adults

Conventional laboratory methods used in virus research have failed to disclose the etiology of most epidemics of acute nonbacterial gastroenteritis Reports that epidemic diarrhea of newborn infants can be transmitted by stool filtrates to young calves await confirmation It is now known that most outbreaks of diarrhea in newborn nurseries are caused by certain strains of *Escherichia coli* The evidence that gastroenteritis can be produced in volunteers by inhalation of pharyngeal washings or stool suspensions is not entirely convincing However gastrointestinal symptoms may be prominent in common respiratory diseases and an epidemic of type 3 adenovirus infection (p 1041) in Sweden was associated with a 40 per cent incidence of diarrhea Many outbreaks of gastroenteritis occur in families and institutions at a time when respiratory diseases are conspicuously absent

Despite the uncertain status of the nonbacterial gastroenteritides Gordon and his associates have shown that two agents presumably viruses can be transmitted to volunteers by the oral but not by the respiratory route Immunity to one agent persisted for at least 15 months in individuals who were fully susceptible to the other Although the clinical and epidemiologic features of these two forms of gastroenteritis overlap considerably it is convenient to classify them as *afebrile* and *febrile* types (Jordan Gordon and Dorrance 1953)

Afebrile Nonbacterial Gastroenteritis ("Viral" Dysentery) The incubation period is usually 2 to 3 days but varies from 1 to 5 days The onset is often abrupt but may be gradual and preceded by malaise anorexia and nausea which almost invariably persist throughout the illness Vomiting can occur on the first day but is not prominent thereafter Crampy abdominal pains of mild or moderate severity may be the first symptom The most characteristic feature is persistent watery diarrhea without blood mucus or pus in the stools Tenesmus is uncommon although many patients have more than 20 bowel movements a day Mild headache and fever up to 101 F a day or two after onset of gastrointestinal symptoms are sometimes present The usual duration of illness is 3 to 4 days but may be as long as a week

Adults recover uneventfully without complications or sequelae Young children can become

inflamed but rarely cause pain or discomfort The papules are usually multiple and occur on any portion of the skin except the palms and soles The only treatment is surgical removal local recurrence is less frequent than is the case with warts

ORF (Ecthyma Infectiosum)

Orf is a viral disease of sheep and goats which takes the form of a benign but lingering infection of the mouth and lips The disease in man usually occurs in herdsmen who contract the infection while force feeding sick lambs Lesions appear on the hands or other exposed areas and consist of papules which rapidly vesiculate and enlarge into hemorrhagic bullae Itching is frequently intense the lesions soon rupture and become encrusted and umbilicated Mild regional lymphadenopathy is usually present but systemic manifestations are rare The lesions subside spontaneously within 2 to 3 weeks unless secondarily infected with bacteria Scarring does not occur and a single attack confers permanent immunity The only diagnostic test is isolation of the virus by inoculation of vesicular fluid into susceptible sheep The appearance of the lesions and a history of contact with lambs should suggest the correct diagnosis but orf is often confused with anthrax sporotrichosis tularemia milker s nodules inoculation tuberculosis and various forms of contact dermatitis

MILKER S NODULES

This is a benign infectious disease of dairy farmers contracted from infected cows It is presumed to be of viral etiology although the agent has not thus far been transmitted experimentally The disease in dairy cattle is world wide and is characterized by indolent ulcers and granulomas of the udder In man lesions appear 5 to 7 days after milking an infected cow they occur mainly on the hands but are occasionally seen on other exposed areas The lesions are often multiple and begin as dark papules which gradually enlarge into firm brownish red or purple nodules from 1 to 2 cm in diameter They are rarely painful or tender and contain no fluid or pus A gray depressed eschar gradually forms on the surface of a red base of granulation tissue and the lesions heal slowly after several weeks leaving no scar The lymph nodes draining the site of infection may enlarge but there are no other local or systemic manifestations Milker s nodules are often confused with cowpox which is caused by an entirely different virus (see p 1062) No specific treatment is available or required

FOOT AND MOUTH DISEASE

This is a highly contagious disease of cattle and other domestic animals caused by the smallest virus known to infect animals or man In the United States rigid quarantine and slaughter of infected animals have confined the disease to a few outbreaks near the Mexican border The rare instances of human infection have resulted from ingestion of meat or dairy products or from exposure to excreta hides or entrails of sick animals In man the illness starts abruptly with fever malaise and headache after an incubation period of 2 to 18 days Initially there is extreme dryness of the mouth followed shortly by excessive salivation and generalized pruritus After several days large clear vesicles appear in the mouth and pharynx and over the palms and soles Rarely the skin is affected elsewhere The lesions of the mucous membranes and skin are painful and soon become shallow ulcers that bleed easily The ulcers heal spontaneously within 2 to 3 weeks leaving no scars The virus can be isolated in guinea pigs by inoculation into the footpad of fluid from the vesicles A complement fixation test is also available for detecting specific serum antibodies in convalescence

VESICULAR STOMATITIS

Vesicular stomatitis is a contagious disease of horses mules cattle and swine Human infection occurs rarely in veterinarians farmers and virologists after an incubation period of 24 to 48 hr In man the disease is characterized by sudden onset with shaking chills high fever headache and prostration The fever and symptoms subside completely after 24 to 48 hr but the same symptoms may recur 3 to 4 days later This second phase of the disease usually lasts a week and is accompanied by the appearance of papular and vesicular lesions in the oropharynx that form superficial ulcers The cervical lymph nodes are often swollen and tender The diagnosis can be confirmed by virus isolation or serologic studies

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feces unchanged or may develop into precysts which in turn develop into mature cysts on meeting conditions outside of the host unfavorable for the parasite

Pathogenesis The trophozoites invade the mucosa extend through the muscularis into the submucosa and produce small flask shaped ulcers which contain yellowish brown necrotic material Elaboration of cytolytic enzymes and perhaps of *hyaluronidase probably aids in this tissue destruction* There is little or no cellular reaction around the ulcers unless they are secondarily infected by intestinal bacteria The entire colon is often involved in the process The cecum ascending colon rectum sigmoid and appendix are involved in that order The inability to produce amebiasis by inoculation of *E histolytica* into animals reared in a germ free environment suggests that symbiosis with normal intestinal bacteria is a *sine qua non* for actual disease production

A delicate host parasite relationship determines whether or not symptoms occur In an early experiment 20 volunteers were fed cysts of *E histolytica* Eighteen became parasitized and passed amebas in the stools Of the entire group however only 4 developed dysenteric symptoms It has been estimated that nearly 90 per cent of persons infested do not have striking symptoms In these the size of the ulcers remains microscopic Small ulcers may coalesce however to form larger ones resulting in any of the diarrheal symptom complexes Amebas which have invaded the colonic mucosa may have any of the following fates (1) They may be completely eradicated (2) maintain an asymptomatic carrier state by virtue of the minute ulcers (3) produce larger ulcers which are symptomatic (4) pass through radicles of the portal veins lodge in the liver and produce hepatitis and/or abscess formation (5) travel via the blood stream or by direct extension to other locations inducing less common disease entities

Epidemiology Amebiasis is world wide in distribution with the highest incidence of the disease in tropical and subtropical regions It is more prevalent in the southern than in the northern parts of the United States It has been estimated that the over all infestation rate in the United States is in the neighborhood of 10 per cent but the true incidence in various locales has not been determined The Chicago epidemic of 1933 attributable to a defective plumbing system in one of the larger hotels attests to the fact that urban areas are by no means immune Servicemen returning from Second World War service in endemic areas and those recently back from Korea are a further potential source of amebiasis However a survey conducted in a Veterans Hospital in the southeastern United States in 1951 revealed a rate of 10 per cent infested with cysts—not in excess of that expected in the population unexposed to endemic areas of infestation

Amebiasis is transmitted from man to man there are no intermediate hosts In areas with good sanitation the principal source of infection is the food handler who passes cysts in his excreta In more primitive areas where human fecal material is used for fertilization of the soil vegetables improperly cooked are a large factor in perpetuating amebiasis Since the trophozoites die rapidly upon exposure to changes in temperature active cases of amebic dysentery are not a menace Upon convalescence and with the beginning of passage of cysts which are much more resistant to external environs these persons then join with the chronic cyst carriers as potential spreaders of the disease Contaminated water supplies and flies may spread the infection

Modes of prevention are concerned with improvement of sanitation with recognition of carriers and their removal from food handling and with education of the general public as to the potential dangers of amebiasis so that milder degrees of amebiasis can be recognized treated and the carrier state prevented

Clinical Features *Dysentery* As mentioned previously the majority of persons infected by *E histolytica* are asymptomatic The commonest clinical syndromes noted are varying degrees of diarrhea

In the usual case amebic dysentery is insidious in onset Vague lower abdominal cramping sensations with one or more loose stools a day are often the first symptoms noted The stools are usually foul smelling and often contain bits of bright red blood and some mucus Vague indigestion a sense of being unwell a low grade fever and alternating periods of constipation and diarrhea are often accompanying symptoms It is not unusual to find that such symptoms have been present intermittently for months or even years before a definite diagnosis is made There is little to note on physical examination except for slight tenderness along the course of the colon and some evidence of weight loss

Acute Amebic Dysentery A less commonly observed variant is acute amebic dysentery Patients so affected have a sudden onset of acute bloody dysentery with frequent stools tenesmus severe abdominal pain and at times vomiting The temperature is elevated at times as high as 105 F During combat conditions of the Second World War it was noted that this picture frequently accompanied acute bacillary dysentery It is possible that in such a situation the bacterial infection activates acute amebiasis in a person who otherwise is a relatively asymptomatic carrier

Asymptomatic Cases In the so called *asymptomatic cyst passer* it is often found on careful an

severely dehydrated requiring parenteral replacement of fluid and electrolyte losses Symptomatic relief of diarrhea is best achieved with tincture of opium (paregoric) given after every bowel movement or every few hours

Febrile Nonbacterial Gastroenteritis The incubation period is 20 to 30 hr The onset is usually abrupt and characterized by moderately severe colic abdominal pain and vomiting Diarrhea is infrequent although there may be an increased number of formed or soft stools Chilliness and cold sweats may be present at the onset and fever of 101 to 103 F headache malaise and prostration are prominent features The illness rarely lasts longer than 48 hr Specific treatment is not available but atropine may relieve the abdominal pain and vomiting

A disorder known as winter vomiting disease appears to be similar in onset duration and clinical manifestations but is more frequently associated with diarrhea It is only mildly contagious and has not been transmitted to volunteers

Laboratory Findings No specific diagnostic procedures are available but stool examination and cultures are helpful in excluding more serious gastroenteritides

Differential Diagnosis Dietary indiscretions excessive ingestion of alcohol and psychologic stress can precipitate vomiting and diarrhea that closely simulate acute gastroenteritis Staphylococcal food poisoning (p 843) invariably has a precipitous onset of severe vomiting and retching ordinarily without fever or diarrhea 1 to 6 hr after ingestion of the incriminated food Salmonella gastroenteritis (p 889) usually has a 12 to 24 hr incubation period and is often associated with systemic manifestations fever and leukocytosis Outbreaks of food poisoning are characterized by explosive and simultaneous occurrence of symptoms in affected individuals without late secondary cases whereas epidemics of viral gastroenteritis begin insidiously usually continue for several weeks and cannot be traced to food or water supplies Mild shigellosis (p 891) may be difficult to differentiate from "viral" gastroenteritis but outbreaks usually result in cases with sustained fever tenesmus and bloody purulent stools that contain pathogenic bacteria

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Section 17 Protozoan Infections

194 AMEBIASIS

Max Michael Jr

Definition The term amebiasis denotes infestation by the protozoan *Endamoeba histolytica* The primary effect of this parasite is on the large bowel but it may also invade the liver and lungs and less commonly the ileum skin brain and pericardium

Etiology *Endamoeba histolytica* infests the intestinal tract of man and of some species of monkeys rats cats dogs and swine A large race of high virulence and a small less virulent race have been described Present evidence however does not indicate that any of the races lack human pathogenicity *Two forms* are recognized the motile (vegetative) or trophozoite and the encysted or cyst When infective cysts are ingested by the host they pass through the stomach unchanged but upon reaching the lower small bowel find conditions that are favorable for excystment Division then occurs each cyst ultimately yielding eight new trophozoites capable of invading the colonic mucosa In the wall of the intestinal tract reproduction takes place by binary fission with liberation of trophozoites These may then invade the host tissue or may pass in the

tially but do not prevent clinical relapse or the carrier state from ensuing It is often necessary to follow one agent with a course of another to effect a real cure Present evidence indicates that best results will be obtained by a course of oxytetracycline (2 Gm a day for 10 days) or a combination of Milibis and chloroquine diphosphate (0 5 Gm Milibis and 0 15 Gm chloroquine diphosphate each t i d for 7 days) An older but still satisfactory regimen consists of carbarsone (0 25 Gm t i d for 10 days) followed by chiniofon (1 0 Gm t i d for 10 days) Emetine which enjoyed wide popularity for many years is now reserved for some cases of extraintestinal amebiasis It is a toxic drug and may produce myocarditis or peripheral neuritis

In the majority of cases diarrhea ceases and symptomatic improvement is striking after the first 2 or 3 days of therapy Lack of symptoms does not constitute cure and the goal of therapy is complete eradication of amebas from the body Careful follow up studies of stool concentrates for at least 6 months are desirable If clinical relapse occurs or cysts reappear re treatment is indicated Whenever liver involvement with the parasite is suspected chloroquine which is effective against amebas in this organ but not against those in the bowel (see below) should be added to the therapy liver abscesses have enlarged and become symptomatic while the patient was receiving drugs effective in the bowel alone (e g oxytetracycline) Treatment of the asymptomatic carrier is the same as for the person with active dysentery The cyst passer must not handle food for others until the stool has become free of parasites

The amebicides are not without toxicity Chiniofon as well as the antibiotics may cause diarrhea which can make evaluation of symptom response rather difficult The toxicity of emetine has been mentioned The iodides may occasionally cause rash and fever and the arsenicals may rarely produce exfoliative dermatitis or liver damage

Hepatic Involvement At any time in the course of infestation of the colon amebas may be carried to the liver In many instances they are destroyed there but in approximately 5 per cent of cases of amebic dysentery disease is manifest in the liver with hepatitis or abscess No clearcut distinction between the two is warranted as they differ only in degree

The amebas gain access to the liver through the portal circulation and localize principally in the right lobe Rarely invasion occurs by way of lymphatics or by direct extension The pathology is characterized by scattered areas of necrosis and degeneration of liver parenchyma with an absence of inflammatory response unless secondarily infected In experimental amebic hepatitis thrombosis of the smaller portal vein radicles is a prominent feature With healing small fibrotic lesions which do not impair liver function result Calcification is rare

Clinical evidence of liver involvement may be apparent without bowel symptoms Only 25 per cent of patients have diarrhea at the time of the liver disease A history suggestive of amebic dysentery weeks or years in the past is obtained in about half the cases Amebas are found in the stools in somewhat less than half the cases The essential point to be remembered is that amebic liver disease can occur without any preexisting or coexisting manifest bowel disease

The clinical states that ensue vary from an acute fulminating hepatitis to a mild indolent abscess In some instances there is sudden onset with chills sweats severe abdominal pain tending to localize in the right upper quadrant nausea vomiting and spasm of abdominal muscles Fever may be as high as 104 F and the leukocyte count over 25 000 The differential count is frequently normal Any of the acute abdominal emergencies such as cholecystitis ruptured viscus and acute pancreatitis may be simulated but a few facts suggest diffuse amebic hepatitis Tenderness is marked over the liver and localized areas of tenderness may be noted Abscess formation is suggested by pain referred to the shoulder some hepatic enlargement low grade fever weight loss and tenderness over the liver A nonproductive cough may be noted Point tenderness in one of the intercostal spaces over the right lobe suggests abscess formation Jaundice and other evidences of impaired liver function are unusual (Abscess may exist with a normal white cell count) Certain roentgenologic features aid in the diagnosis of abscess formation Elevation of the right dome of the diaphragm and obliteration of the cardiophrenic angle and of the anterior costophrenic angle on lateral view are suggestive of abscess formation Aspiration of the contents of an abscess yields a thick chocolate colored material which has been likened to anchovy paste It is rare to find amebas in the pus since they are principally in the wall of the abscess

The response to treatment of amebic liver disease serves as an important diagnostic tool Chloroquine diphosphate which is highly concentrated in the liver has proved to be quite effective against amebas in this organ It is rapidly becoming the drug of choice replacing emetine which though potent is toxic The dosage is 1 0 Gm a day for 2 days followed by 0 5 Gm a day for 21 days Its effects on the bowel disease are not of a high order hence one of the agents effective for the bowel disease (e g oxytetracycline) is given concomitantly in order to attack any parasites which may be in

amnesis that vague digestive complaints and an occasional mild diarrhea have been noted by the patient The cyst carrier is more than a potential public health menace He may on occasion revert to a stage of active dysentery Furthermore any of the serious metastatic manifestations of amebiasis may develop in such asymptomatic individuals

Amebic Granulomas Amebic granulomas the so called *amebomas* which are single or multiple may be located in any region of the large bowel particularly in the cecum They usually develop in long standing cases of amebic dysentery It is important that they be recognized and differentiated from carcinoma which they may simulate Surgical intervention before antiamebic therapy is administered is attended by a high mortality

Diagnosis Amebic dysentery should be considered in every case of diarrhea The character of the stool is often of considerable aid in the diagnosis In the usual type of amebic dysentery it is soft or even loose and watery Flecks of mucus and bright blood frequently cling to the outside of the stool Microscopic examination must be performed on a fresh warm stool The cellular exudate in the feces is predominantly mononuclear in contradistinction to the polymorphonuclear exudate of bacillary dysentery *Several examinations may be necessary* to find the parasites Care in choosing flecks of bloody mucus for study is rewarding In such bits of exudate motile amebas often with ingested red blood corpuscles will be seen The amebas move actively about the stage by thrusting out pseudopodia of clear cytoplasm into which may flow red corpuscles and other particulate matter The motile forms of *E coli* a nonpathogenic inhabitant of the bowel may be confused with *E histolytica* The former are only sluggishly motile do not throw out clear pseudopodia and never contain ingested red corpuscles Motile forms not previously evident may appear in stools following a magnesium sulfate purge If parasites are not found cyst forms should be looked for in a stool concentrated with zinc sulfate and stained by appropriate methods *Endamoeba histolytica* may be cultured from stools by use of special media In the hands of qualified workers this method increases the chances of obtaining positive results and is especially efficacious for recognition of the cyst passer

The *proctoscopic examination* yields valuable information In the early stages of the disease small shallow ulcers often covered with mucous flecks will be seen Punctate hemorrhage and hyperemia may be noted The intervening mucosa usually appears normal As the disease progresses the ulcers become deeper and develop slightly raised edges giving the appearance of bomb craters They may be multiple and small or single and large Material obtained from one of the ulcers either by cotton swab or by aspiration is usually swarming with motile trophozoites Lesions will not be seen in all cases since involvement of the right side of the colon may constitute the sole lesion

The *complement fixation test* for amebiasis offers potential diagnostic and therapeutic aid However the difficulty in preparing a stable antigen has led to diverse results Many laboratories have so standardized the procedure that less than 10 per cent of patients with amebic dysentery have a positive test whereas 85 per cent of those with hepatic amebiasis have a positive test It reverts to negative upon eradication of the amebas The implications of the test are apparent A mild normocytic anemia is noted in chronic cases The white blood count is slightly elevated in mild cases and may be as high as 30 000 in the cases of the acute type

Differential Diagnosis All causes of diarrhea enter into the differential diagnosis The simple diarrheas whether caused by *Salmonella* viruses or enterotoxins or whether of functional or unknown causes may simulate the milder forms of the disease Moreover acute amebic dysentery can simulate acute bacillary dysentery in onset and in course In this respect it should be mentioned that large *mononuclear cells which appear in the fecal exu*date in bacillary dysentery may be confused with amebas Ulcerative colitis offers the chief difficulty in differential diagnosis from the usual type of amebic dysentery however its chronicity proctoscopic and radiologic appearance and lack of response to antiamebic therapy are aids in the differentiation Mucous colitis regional enteritis and carcinoma of the large bowel are other entities requiring consideration In all cases in question careful and repeated stool examinations adequate proctologic examination and response to therapy will usually establish or exclude the diagnosis of amebic dysentery

Treatment It cannot be said categorically that there is a drug of choice in the treatment of amebiasis The many drugs available can be grouped into five classes A drug from a single class is often effective whereas others are combined with agents from one or more of the other groups to achieve effects The groups with representatives of each are (1) arsenicals (carbarsone Milibis) (2) halogenated quinolines (Diodoquin chiniofon Yatren) (3) antibiotics (oxytetracycline bacitracin) (4) ipecac derivatives (emetine) and (5) aminoquinolines (chloroquine) The ideal therapy terminates the acute attack promptly eradicates parasites from the bowel wall and thus prevents the chance of further relapse of the patient or of a menacing carrier state Many drugs fall short on the last two items They eradicate the amebas in

Man is the intermediate host and the mosquito the definitive host In man after a stage of exo-erythrocytic development the parasites reproduce asexually in circulating erythrocytes They first appear in the red cells as *ring forms* after several divisions daughter cells (*merozoites*) fill the corpuscle which ruptures and releases them to parasitize additional erythrocytes With repetition of this cycle some of the red cells become filled with sexual forms (*gametocytes*) these do not induce cell lysis and are unable to undergo further development unless ingested by an appropriate mosquito during a blood meal In the stomach of the mosquito fertilization occurs and the resulting *ookinete* encysts on the outer surface of the stomach and releases myriads of *sporozoites* These migrate to the salivary glands and if inoculated into a human subject lead to repetition of asexual multiplication There is variation in this cycle among different species and several intermediate developmental stages occur

The asexual cycle in the erythrocyte requires 36 to 48 hr for *P falciparum* 48 hr for *P vivax* and *P ovale* and 72 hr for *P malariae* The periodicity of febrile paroxysms in infections by the different species coincides with the cyclic discharge of merozoites and infestation of new cells

The incubation period between bite of an infected mosquito and onset of symptoms is 10 to 14 days in vivax and falciparum malaria and 18 days to 6 weeks in quartan infections

There is good evidence for the existence of several strains of each species of human malarial *Plasmodium* and greater virulence of some strains is suggested by the consistent severity of the clinical illnesses which they produce

Epidemiology Malaria survives only in areas where the mosquito and the infected human populations remain above a *critical density* for each These critical densities are interdependent but either may fluctuate in a given area Control measures are directed toward reducing both populations to levels that are too low for the infection to survive Important procedures include drainage or filling of breeding areas use of residual insecticide sprays (this has largely replaced the use of oil or other antilarval measures) screening use of skin repellents effective treatment of cases and large scale suppressive drug programs in some human populations

The disease remains highly prevalent in many parts of the world and it is estimated that more than two hundred million cases occur annually An active international cooperative program of malaria control has resulted in a significant decline in the incidence of the disease since 1945 and despite the enormity of the remaining problem many areas in South America southern Europe and Asia are now almost free of the infection

Manifestations *General* There is some variation in the clinical diseases produced by the different plasmodia but in all chills fever excruciating headache muscle pains splenomegaly and anemia are common Herpes labialis is very frequent but usually appears only after the infection is well established Hepatomegaly and mild icterus are often observed especially in estivo autumnal infections

The hallmark of the disease is the malarial *paroxysm* which recurs at regular intervals in all but falciparum infections The typical paroxysm begins with a rigor that lasts 20 to 60 min ("cold stage) followed by a "hot stage" of 3 to 8 hr with fever of 104 to 107 F The "wet stage" consists of defervescence with profuse diaphoresis which leaves the patient weak and exhausted

First attacks of malaria are often severe but with repeated episodes symptoms become milder although debilitation may be progressive There is good evidence for the development of immunity to malaria but it is of a low order in so far as protection against reinfection is concerned Negroes are peculiarly insusceptible to *P vivax* infections

Tertian Malaria (P Vivax or P Ovale) This infection is rarely fatal although relapses are common and it is the most difficult to cure A prodrome of myalgia headache chilliness and low grade fever for 48 to 72 hr heralds the onset of the typical paroxysms Transient urticaria sometimes precedes each of the paroxysms which occur on alternate days unless there has been double infection with two maturation cycles in which case daily chills can occur Such double infections usually synchronize" within a week and paroxysms then follow the classic tertian pattern

Quartan Malaria (P Malariae) In this infection paroxysms occur every third day unless multiple infection alters the cycle initially and chills occur on 2 out of 3 days or even daily until the cycles synchronize Quartan malaria is usually a more disabling infection than tertian but responds well to treatment Edema albuminuria and hematuria (not hemoglobinuria) a clinical state similar to acute hemorrhagic nephritis occasionally appear during the course This complication should not be confused with *blackwater fever*

Estivo Autumnal Malaria (P Falciparum) This is a severe disease The organisms are present in enormous numbers and there is a striking tendency for agglutinated masses of parasitized erythrocytes to block capillaries throughout the body producing localizing signs that mimic many other diseases There is often "asynchronization" of the cycle of multiplication typical malarial paroxysms occur

this location Within 3 to 5 days of commencing therapy dramatic changes are usually noted The temperature returns to normal leukocytosis subsides pain and tenderness decrease remarkably the liver size decreases and a sense of well being returns In those cases with persisting abscess formation as evidenced by continuing localized tenderness or an abnormal bulge in the diaphragm the contents must be evacuated while chloroquine therapy is continued The aspiration is performed with an 18 gauge needle at the point of maximum tenderness over the liver One aspiration usually suffices but continuing pain and localizing signs are indications for another attempt At times it is difficult to decide whether to aspirate since the presence of abscess cannot be definitely established however it is a good general rule to aspirate when in doubt In view of its faster acting properties emetine should be given to the gravely ill patient or to the patient whose abscess has been entered surgically It should also be used when the abscess has not responded to chloroquine therapy Emetine hydrochloride is administered subcutaneously in doses of 0 065 Gm daily for 7 to 10 days If the abscess is infected secondarily with pyogenic bacteria appropriate antibacterial chemotherapy should be instituted

If abscesses are not treated properly the patient may become cachectic and die of infection On the other hand the abscess may rupture into the lungs producing any of the pulmonary syndromes

Pleuropulmonary Involvement Direct extension into the pulmonary tract occurs in approximately 15 per cent of cases of amebic liver disease The right lung and pleural cavity are the areas involved Rarely the lesions may be metastatic without any detectable evidence of preexisting liver disease When the process of extension is a gradual one and the pleural surfaces have adhered to each other the abscess penetrates either directly into the lung causing an abscess or directly into a large bronchus producing a hepatic bronchial fistula If the process is more acute extension into the pleural cavity with empyema results These three conditions occur with about equal frequency

The signs and symptoms of pleuropulmonary amebiasis are similar to those of suppurative disease in these areas In some cases the first indication of the amebic nature of the disease is the expectoration of copious amounts of a dark chocolate brown pus which may taste like liver As indicated most of the patients have accompanying liver involvement and in them pulmonary invasion is manifested by cough septic fever and localized chest pain Roentgenologic demonstration of elevation of the right dome of the diaphragm with overlying pulmonary infiltration is highly suggestive of amebiasis In the lateral view a triangular area of pulmonary infiltration overlying a bulging diaphragm is helpful in diagnosis

Management of pleuropulmonary amebiasis is similar to that for amebic liver abscess Frequent bronchoscopic drainage may be indicated for localized lung abscesses With secondary infection antibacterial chemotherapy should be instituted

Other Manifestations *Endamoeba histolytica* may involve any region of the body Other rarer manifestations include pericarditis resulting from direct extension from the liver peritonitis secondary to rupture of liver abscess urethritis vaginitis and brain abscesses which are metastatic Cutaneous lesions resulting from draining sinuses infected with amebas are exceedingly painful and destructive Their response to therapy is satisfactory Otherwise unexplained generalized urticaria results from parasitism by amebic cysts in a small number of cases The urticaria abates upon eradication of the amebas

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195 MALARIA

Ivan L Bennett Jr

Definition Malaria is a protozoan disease transmitted to man by the bite of *Anopheles* mosquitoes Although it is now rare in the United States it is probably the most prevalent infectious disease throughout the world Malaria is characterized by rigors fever splenomegaly anemia and a chronic relapsing course

Etiology The causative organisms are protozoa of the genus *Plasmodium* The four species known to infect man do not produce disease in lower animals although many other species affecting animals and birds are known *Plasmodium vivax* causes tertian malaria *P malariae* causes quartan malaria *P falciparum* causes malignant tertian (estivo autumnal) malaria *P ovale* causes ovale tertain malaria a relatively rare and mild illness

narcotics) should suggest the disease Splenomegaly is an almost invariable finding its absence is strong evidence against malaria Leukocytosis is not a feature of malaria

The confusion of *P falciparum* malaria with various disorders of the brain lung or intestine has been mentioned

While final cure of malaria may be difficult particularly in *P vivax* infections almost all cases will respond symptomatically to quinine or one of the newer antimalarial drugs and failure of response to a therapeutic trial argues strongly against the diagnosis

Treatment The use of appropriate chemotherapy can suppress symptoms in individuals exposed in endemic areas or cure malarial infection completely The development of new antimalarial drugs has led to replacement of quinine and Atabrine (quinacrine) as the agents of choice although both will undoubtedly continue to be used for many years A good dosage schedule for quinine sulfate is 1 0 Gm orally t i d for 2 days and 0 6 Gm daily for 1 week Quinine dihydrochloride can be given intravenously (not intramuscularly) in a dose of 10 ml of a 3 per cent solution every 4 hr until oral medication can be taken

The oral dosage of Atabrine is 0 2 Gm every 6 hr for five doses and 0 1 Gm t i d for 6 days Quinacrine dihydrochloride can be given intramuscularly (*not* intravenously) in a dose of 0 2 Gm every 6 hr until oral therapy can be tolerated

The initial administration of 600 mg chloroquine (Aralen) base followed by 300 mg 6 hr later and then 300 mg daily for 2 days usually produces complete subsidence of *P falciparum* and *P ovale* infections For *P vivax* and *P malariae* infections another drug should be combined with chloroquine to avoid relapse common in both types Fifteen mg primaquine base by mouth daily for 14 days is the best regimen relapse after treatment by this combination is extremely rare

The suppressive dose of chloroquine is 300 mg once weekly General supportive measures fluids good diet symptomatic relief of headache or other pains and occasionally blood transfusions are all important

Specific antimalarial drugs should be withdrawn in patients with blackwater fever

Overdosage of quinine produces cinchonism with tinnitus as an early manifestation Occasional instances of mild hemolysis attributable to it have occurred and it is a cause of allergic purpura (non thrombocytopenic) and drug fever

Atabrine causes a yellow staining of the skin Given intravenously it usually produces circulatory collapse Primaquine produces hemolytic anemia in many Negroes apparently because of an inborn error of erythrocyte metabolic activity (see p 1164) Chloroquine rarely causes any reaction other than occasional mild desquamation and itching

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196 LEISHMANIASIS

Edward S Miller

Definition and Etiology Protozoa of the genus *Leishmania* cause several different diseases which are referred to collectively as leishmaniasis *Visceral leishmaniasis* is a generalized systemic infection commonly referred to as *kala azar* caused by *Leishmania donovani* Two types of *cutaneous leishmaniasis* are generally recognized *oriental sore* is due to *L tropica* *American cutaneous* or *mucocutaneous leishmaniasis* is caused by *L braziliensis*

In vertebrate hosts the parasites lie within reticuloendothelial cells and take the form of nonflagellated oval organisms (Leishman Donovan bodies) 2 to 3 μ in diameter In the body of the sandfly they become flagellated The several members of this genus are indistinguishable morphologically and culturally but they differ antigenically and the diseases to which they give rise are distinctive Persons recovering from kala azar or oriental sore possess a considerable degree of homologous immunity On the other hand the two diseases do not immunize against each other

Epidemiology and Pathogenesis Leishmaniasis is transmitted by various species of biting sandfly (*Phlebotomus*) vectors which become parasitized by sucking the blood of infected hosts and which subsequently transmit the infection by regurgitating into the bite wounds of succeeding victims These diseases are endemic only in tropical and semitropical regions where sandflies are found The flies feed chiefly at night and are found mostly in rural areas Organisms are present in the open lesions in oriental sore and in American leishmaniasis and these diseases can also be transmitted by contact

but continuous remittent or irregular fever is present in many cases and illness can be constant

The course of uncomplicated estivo autumnal malaria is ordinarily milder than that of tertian or quartan infections However capillary blockage by the parasites can give rise to serious even fatal complications and it is this feature of *P falciparum* infections that accounts for the protean manifestations of estivo autumnal malaria and the relatively high morbidity and mortality associated with it Depending upon the organ system involved several so called *pernicious syndromes* are seen *Cerebral malaria* can lead to hemiplegia convulsions delirium hyperpyrexia coma and rapid death When the *pulmonary* circulation is involved there may be cough and blood streaked sputum leading to confusion with many other diseases of the lung The splanchnic capillaries can be obstructed with consequent vomiting abdominal pain simulating appendicitis severe diarrhea or melena Such patients are sometimes thought to have bacillary dysentery or cholera Fever in these disorders may be low or absent Indeed in patients with predominantly gastrointestinal manifestations there are usually cold clammy skin hypotension profound weakness and repeated syncopal attacks so called *algid malaria*

Blackwater Fever This is a disorder that occurs in association with malaria particularly and perhaps only with *P falciparum* infections The usual attack begins with a rigor and fever followed by massive intravascular hemolysis icterus hemoglobinuria collapse and often acute renal failure and uremia The pathologic findings in the kidney are typical of lower nephron nephrosis with necrosis of tubules and hemoglobin casts The mortality is 20 to 30 per cent and survivors are very likely to experience hemolytic episodes with subsequent malarial infections

Although blackwater fever is often classified as one of the pernicious complications of estivo autumnal malaria its etiology is obscure There is nothing to suggest that capillary blockage by the parasites produces the renal disturbance *P falciparum* has not been shown to elaborate a hemolysin and in many patients with blackwater fever parasitemia is absent Conflicting evidence suggests a possible role of therapy with quinine in the hemolysis there are good observations to the effect that antimalarial drugs in general neither speed recovery from an attack nor influence the outcome Tender splenomegaly is a constant finding and this has led to the suggestion that the hemolysis is a result of hypersplenism In the past cardiac decompensation has been the usual cause of death in patients with blackwater fever It is probable that the heart failure resulted from overhydration in ill advised attempts to flush the kidneys of oliguric patients The institution of an appropriate regimen for acute renal failure (see p 1367) should reduce the fatality rate considerably

Complications In addition to the several complications already mentioned others deserve comment Rupture of the spleen is relatively rare but malaria is by far the commonest cause of spontaneous rupture and predisposes to traumatic rupture of this organ

Chronic malaria or repeated infection in an endemic area leads to anemia debility and cachexia Secondary bacterial infection is often the immediate cause of death in such patients Bacillary dysentery cholera and pyogenic pneumonia are common Tuberculous foci often extend in malarial patients and miliary tuberculosis is occasionally observed

Laboratory Findings The blood leukocyte count is usually low but may be normal The erythrocyte sedimentation rate is elevated Plasmodia are demonstrable in smears of peripheral blood from the vast majority of patients with symptomatic malaria When the disease is suspected appropriately stained blood films should be examined diligently For the inexperienced examiner a thin smear of fingertip blood on a clean glass slide should be stained with Wright Giemsa or Hastings stain Parasitized erythrocytes are most frequent at the edges of a smear extracellular parasites are not found Thick smears should be thoroughly dried and stained with diluted Giemsa or Field stain This method has the advantage of concentrating the parasites but artefacts are numerous and correct interpretation of these preparations requires much experience

The morphology of the four species of plasmodia that infect man is specific enough to allow identification in blood smears The details of this morphology are available in textbooks of parasitology The parasitized erythrocytes in *P vivax* infections are usually enlarged and hypochromic in *P malariae* infections they are small and hyperchromic and in *P ovale* infections the red cells containing parasites are oval

There is no advantage over blood of material obtained by splenic or sternal puncture The administration of epinephrine with the idea of dislodging parasites by producing contraction of the spleen has been advocated but results are irregular There are no reliable diagnostic serological tests

Diagnosis The most important diagnostic test is the search for parasites in peripheral blood History of residence in an endemic area previous attacks of malaria typical malarial paroxysms or some artificial exposure (blood transfusion addiction to

used systemically the trivalent compounds are more effective Tartar emetic may be given in a dose of 0 1 Gm intravenously on alternate days for a total of 12 to 15 injections

The treatment of the American form of cutaneous leishmaniasis is similar to that of oriental sore Antimonials are only moderately effective but nevertheless essential when mucous membrane lesions are present tartar emetic is the drug of choice

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197 TOXOPLASMOSIS
Harry A Feldman

Definition Toxoplasmosis a disease of increasing importance results from infection with an intracellular protozoan parasite *Toxoplasma gondii* which is widely distributed among mammals and birds In man it may produce acquired or congenital illness The former is frequently unapparent

History First demonstrated in 1908 by Nicolle and Manceaux in a North African rodent the gondi and in the same year by Splendore in Brazil *Toxoplasma* was not definitely related to human disease until 1939 when Wolfe Cowen and Paige described infantile cases of encephalomyelitis which had resulted from congenital infections with the parasite Several cases of the acquired disease were reported shortly thereafter but interest in *Toxoplasma* was limited and it was considered to be important principally as the causative agent of a rare congenital di ease The disease producing capabilities of the parasite have become more evident in recent years as the result of the almost simultaneous descriptions of skin complement fixation and dye tests These have been utilized extensively enough to make it apparent that *Toxoplasma* frequently infects man and animals and that congenital

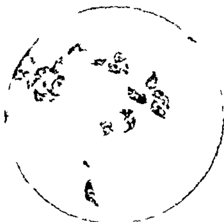


FIG 149 *Toxoplasma* in Wright stained impression film (×1200)

toxoplasmosis is only a segment of a broad relatively common disease spectrum

Etiology *Toxoplasma gondii* is considered to be a protozoon All strains regardless of source appear to be antigenically similar and of the same species The organism measures about 3 0 by 6 0 μ and may appear crescentic oval or round (see Fig 149) It divides by binary fission and is best stained with either Wright or Giemsa stain *Toxoplasma* an obligate intracellular parasite is unique in that it may infect any mammalian or avian cell except erythrocytes It can be maintained in tissue culture or embryonated eggs but does not multiply in the absence of living cells The parasite is readily sedimented by centrifugation Under special conditions it may be stored in the frozen state but ordinary freezing kills the organism

Laboratory Diagnosis A specific diagnosis may be made by the application of serologic methods by demonstrating the organism in smears or by isolating it in mice *Toxoplasma* may be seen in Wright or Giemsa stains of the sediments of spinal or ventricular fluids or occasionally in histologic sections of biopsied lymph nodes or muscle obtained during the active phase of the illness The laboratory mouse is the animal of choice for attempting isolations and may be inoculated with spinal fluid sediment (when acute central nervous system signs are present) or emulsions of fresh tissue At least three blind passages should be made with brain and spleen emulsions before considering the attempt a failure

Serum antibodies may be detected with either the dye or the complement fixation test As is true of serologic procedures in general the results are most meaningful when a rising titer is demonstrated Dye test antibodies seem to develop early and persist for many years possibly for life Complement

It is possible that kala azar occasionally may be transmitted directly from man to man also since the protozoa are sometimes found in nasal secretions pharynx urine and feces of patients Human beings serve as the major reservoir of leishmaniasis Dogs are also of importance in certain Mediterranean areas and in China and naturally infected rodents and other animals are found in other parts of the world

Manifestations *Kala-azar* This disease is prevalent in India China North Africa and countries bordering the Mediterranean A few cases have been observed in South America (Brazil Argentina Bolivia and Venezuela) The incubation period is usually from 2 to 4 months Onset may be gradual or abrupt and the clinical course evolves slowly over a period of months Irregular bouts of fever often with daily double spikes eventually are followed by loss of weight and strength hyperpigmentation of the skin painless hepatomegaly splenomegaly peripheral edema and sometimes lymphadenopathy The bone marrow is hyperplastic and its function is disturbed with reduction of the total leukocyte count to less than 4 000 per cubic millimeter agranulocytosis with its attendant complications is occasionally seen There are a moderate to severe normocytic and normochromic anemia and some diminution in the platelet count Bleeding may occur from the nose gums or intestinal tract or into the skin Liver function test results are frequently abnormal in cases of more than 3 months duration The serum albumin is decreased while the globulin content rises sharply Hyperglobulinemia can be demonstrated readily by means of the formol gel (Napier s aldehyde) and antimony tests Unless treated kala azar is fatal within 2 years in 75 to 95 per cent of cases Patients who recover sometimes develop unusual dermal lesions after a lapse of a year or more The lesions may appear anywhere on the body and are pleomorphic in character including nonulcerating hypopigmented macules nodular and erythematous eruptions verrucous growths and papillomas

Oriental Sore This disease is found in India the Near East Turkestan and the Mediterranean countries The incubation period varies from 2 weeks to as long as 3 years usually it is several months It is manifested by a localized granulomatous ulceration of the skin without pain or constitutional symptoms Lesions may be single or numerous and occur chiefly on the exposed surfaces of the body A typical sore begins as a pruritic erythematous papule gradually enlarges to a diameter of 4 to 8 cm ulcerates in the center and becomes secondarily infected with pyogenic organisms The crater fills with a discharge or a scab and is surrounded by a red indurated rim Even if untreated it heals in approximately a year leaving a smooth but conspicuous scar

American Cutaneous and Mucocutaneous Leishmaniasis (Espundia) This disease is found in tropical regions of Central and South America In it too there are one or more cutaneous granulomas similar to those of oriental sore and with a similar incubation period and clinical course However in as many as one fifth of patients serious metastatic mucous membrane manifestations appear in the form of eroding or nodular granulomatous lesions in the mouth nose pharynx larynx and trachea Rarely the genitalia and the eyes are involved The mucous membrane lesions usually appear months or years after the cutaneous lesions have already healed They progress slowly produce great pain disfigurement and debility and rarely heal spontaneously

Laboratory Diagnosis Specific diagnosis in leishmaniasis is established most readily by identifying the parasites in stained smears In kala azar they are most likely to be found in material aspirated from bone marrow or spleen they can also be found in liver lymph node cutaneous lesions and the leukocytic layer of blood In the cutaneous forms of the disease the organisms are present in scrapings of the local lesions or in the lymphatic structures which drain them Leishmaniae can be cultured from all these sources on special artificial media In espundia an intradermal skin test (Montenegro s test) is usually positive Certain hematologic and blood chemical changes occur in kala azar as outlined above

Treatment Visceral leishmaniasis responds very favorably to treatment with pentavalent antimony compounds including Neostibosan Solustibosan urea stibamine and a newer preparation called Pentostam An average course of treatment for an adult consists of 6 0 ml Pentostam intravenously daily for 6 days A group of drugs known as aromatic diamidines (including stilbamidine and pentamidine) are also potent therapeutic agents Because of their toxicity they are used only in patients resistant to antimonials Post kala azar dermal lesions are rather resistant to treatment and may require several courses of antimonials Diamidines are valueless

Therapy of oriental sore is somewhat less effective though healing eventually occurs spontaneously even in the absence of treatment Secondary pyogenic infection must be eradicated by appropriate use of antibiotics If the lesions are few in number they may be treated locally by the application of carbon dioxide snow or by periodic infiltration with a solution of berberine sulfate Pentostam emetine hydrochloride or quinacrine hydrochloride If the sores are numerous antimonials should be

Treatment There is good evidence in experimental infections that a combination of sulfonamide and 5-p-chlorophenyl 2 4-diamino-6-ethylpyrimidine (Daraprim) is somewhat better than sulfonamides alone Combinations of sulfadiazine or triple sulfonamides and Daraprim have been reported to yield excellent results in some cases of uveitis and to have affected others not at all The data on the effectiveness of this treatment in systemic toxoplasmosis are inadequate The combination is not specific for toxoplasmosis and the patient s response cannot be interpreted as proving or disproving a particular diagnosis The sulfonamide should be administered in the usual dosage along with 50 mg of Daraprim daily The dose of Daraprim probably ought to be decreased after 2 weeks to 25 mg One month of treatment constitutes an adequate trial Since Daraprim may induce severe leukopenia frequent leukocyte counts should be obtained during therapy and medication withdrawn if the leukocyte count becomes abnormal

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Section 18 Diseases Caused by Worms

Gustave J Dammin

Progress in immunology epidemiology pharmacology and other fields has continued to improve our methods of diagnosis treatment control and prevention of the diseases caused by the helminths In the following chapters the effectiveness of Atabrine chloroquine and piperazine will be described More effective methods of field control of vectors have been devised as well as means of individual prophylaxis as in schistosomiasis Clinical and laboratory correlation has led to better definition of such entities as visceral larva migrans (Beaver) and pernicious tapeworm anemia" (von Bonsdorff) Important epidemiologic information has been gained from the work of Rausch on the life cycle and distribution of *Echinococcus multilocularis* in Alaska Publications have described the knowledge pertaining to the metabolism of the helminths and have helped to disseminate information on the important advances in therapy Contributions to these areas are being made by Weinstein and Weller on the in vitro development of larvae to the adult stage However there are other than the immediate medical problems which face the populations of these developing countries most of them tropical, where the helminthic infections are most prevalent. The poor economic status is reflected as well stated by Chandler by the need for "proper food, since malnutrition not only causes disease per se but is a very large factor in ability to fight other diseases and education because only by knowing what is dangerous and why can mankind help to win in the struggle with disease" The magnitude of the problem posed by these diseases has been well described It has been estimated that there are over 2,200 000 000 helminthic infections in the current world population of somewhat less than 2,200 000 000 The direction which control should take is emphasized by the observation that man has acquired over four fifths of these infections because of "ineffective insulation from his own excretory products" (Stoll)

The prevalence of helminthic disease in tropical areas is dependent in varying degree upon the following factors (1) the presence of appropriate vertebrate and invertebrate hosts (2) the higher temperature and humidity (3) poor personal hygiene (4) poor environmental hygiene and (5) particular racial food habits Some of these infections as they are observed in adult residents of endemic areas are usually mild and often asymptomatic This differs from the clinical picture produced in the initially exposed, in whom the infec-

fixing antibodies develop more slowly and disappear more rapidly Thus if a high dye test titer (1 256 or more) and a negative complement fixation re action are encountered one may be dealing with either an early acute infection or the residual sero logic status of past infection

An addition to the knowledge of the dye test is of special interest A positive reaction requires the presence of a heat labile serum factor It has now been demonstrated that this heat labile sub stance is in the properdin system Properdin all four components of hemolytic complement and magnesium are required This is the first instance when presence of the properdin system has been shown to be necessary for the action of a specific antibody

A skin test is available and may be performed with either antigen prepared from mouse peritoneal fluid or embryonated eggs The reaction is of the delayed type and cross reacting antigens have not been identified The egg antigen is preferable be cause suitable control material is available There are two drawbacks to the test as a diagnostic aid in an individual case (1) the number of reactors in the general population is large and (2) serum antibodies have been demonstrated in nonreactors If this test has any value it is in surveys where it may provide an index of the frequency of previous infections in a given area

Epidemiology Surveys performed with the skin and dye tests indicate that *Toxoplasma* infections are widespread About one half of the adult popu lations of Cincinnati Ohio and Syracuse N Y have been found to react positively

The dye test is a sensitive indicator of antibody Using this test it has been determined that ap proximately 33 per cent of the populations of a number of American cities and Haiti 63 per cent of Hondurans and 70 per cent of Tahitian natives are positive In contrast none of 20 Alaskan Eski mos was found to have antibodies and only 4 per cent of Navaho Indians and 11 per cent of a group of Icelanders had significant amounts of antibody Similar studies have been conducted among various animal species antibodies are especially frequent among dogs cats swine sheep goats guinea pigs and to a lesser extent rabbits and pigeons Al though the full significance of these findings re mains to be determined it is clear that serologic evidence indicates that infection with *Toxoplasma* may be abundant in man and many of his animal associates It must be emphasized that variations in prevalence are to be expected among all species The mode of transfer of parasites from animal to animal or to man is unknown there is no evidence for human to human transfer Human infection ap parently may be contracted in any season and with equal frequency by the two sexes

Clinical Manifestations Human infections with *Toxoplasma* may be either congenital or acquired On the basis of survey data referred to above it appears that acquired infections are frequently unapparent

An infant congenitally infected with *Toxoplasma* may be born prematurely or at term as a stillbirth or with an active infection manifested by various combinations of fever icterus rash hepatomegaly splenomegaly chorioretinitis convulsions and xan thochromic spinal fluid The newborn infant may have none of these signs but some time later hydro cephaly or microcephaly chorioretinitis convul sions psychomotor retardation and cerebral calcifi cation may be noted either singly or in combination A fatality rate of 11 per cent was noted in one series of 141 cases of congenital toxoplasmosis Among the more important evidences of disease in these children chorioretinitis was present in 94 per cent while 59 per cent had cerebral calcifica tions 45 per cent had psychomotor retardation and approximately half had either hydro or micro cephaly 39 per cent had convulsive episodes Thus the majority of patients had some permanent dam age The mothers of congenitally damaged offspring ordinarily are unaware of having had any specific illnesses during the pregnancy These women may undertake future pregnancies without fear of a recurrence in another child

In the proved cases of acquired toxoplasmosis the clinical features have shown considerable varia tion but certain manifestations are being recognized as suggestive of this disease Maculopapular rashes are not infrequent soon after the clinical onset of the illness and tend to disappear in 3 or 4 days Lymphadenopathy is common and local nodes may be so prominent as to suggest the possibility of Hodgkin s disease Encephalitis may be present alone or in combination with other manifestations Myalgias arthralgias myocarditis and pneumonitis also have been noted Siim has described a syn drome which resembles infectious mononucleosis in that lymphadenopathy lymphocytosis with atypi cal lymphocytes and negative Paul Bunnell reac tions may be present He has demonstrated parasites in lymph nodes removed from such patients some of whom have afebrile courses

Toxoplasma now have been isolated from cases of granulomatous uveitis presumably the result of acquired infections The proportion of such cases which is caused by *Toxoplasma* remains to be de termined and is still the subject of considerable investigation

There is still no reliable information concerning the incubation period recovery and mortality rates average duration of illness or residual defects re sulting from acquired toxoplasmosis Cerebral calci fications do not appear to follow this form

semble those produced by bacterial and other microbial agents As adults helminths do not multiply in the human host In this form their presence is usually made known by effects which are primarily mechanical The lumen of a hollow viscus or a duct system may be occluded (e g ascariasis fascioliasis) penetration of the intestinal wall to obtain a blood meal may lead to extensive blood loss (e g hookworm) or residence in the wall of a hollow viscus intra or extravascularly may lead to ulceration and blood loss (strongyloidiasis schistosomiasis) As larvae some helminths produce symptoms during penetration of the skin and migration to their site of definitive development There is a similarity between helminthic and microbial infections with reference to the immunologic response of the host In both precipitins complement fixing skin sensitizing and neutralizing antibodies have been demonstrated Tests for immunologic response have diagnostic value in trichinosis *Echinococcus* disease filariasis and schistosomiasis

Attention is focused on the helminthic diseases of man when because of war or other circumstances troops stationed in endemic areas are exposed to these hazards and there is danger of having new or more virulent forms of disease brought by servicemen to nonendemic areas In American army personnel during the Second World War there were reported 2 151 hospital admissions for filariasis and 1 636 for schistosomiasis primarily japonica but the number of infections was undoubtedly considerably greater The number of military personnel contracting hookworm infections in some endemic areas was large but difficult to estimate Because of the presence in the United States of appropriate mosquito hosts the possibility exists that filariasis may again be established here A species of *Tropicorbis* capable of acting as intermediate host for *Schistosoma mansoni* has been encountered in Louisiana More likely is the establishment of *Ancylostoma duodenale* in the southern United States by those returning from the Pacific and Asiatic areas of combat The Korean War kept alive an interest in these problems However as one views the scope and methods of instruction used in the teaching of the helminthic and parasitic diseases in general it is apparent that these diseases are not recognized as the global problems they represent Nor are these diseases recognized as unique problems in host parasite relationships and ecology These aspects should be stressed The importance given these diseases in the curriculum should not be related to their importance in our immediate populations

The important helminths are members of the phyla Platyhelminthes and Nemathelminthes The diseases they produce and their habitats in the human host are tabulated on page 1118

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198 INTESTINAL NEMATODES

Gustave J Dammin

HOOKWORM DISEASE

Definition Hookworm disease is a symptomatic infection caused by *Ancylostoma duodenale* and/or *Necator americanus* Asymptomatic infection may be simply termed *hookworm infection* and the individual with such infection a *carrier*

Etiology *Ancylostoma duodenale* also known as the Old World hookworm possesses four prominent hooklike teeth in its adult stage The male measures about 1 cm in length and presents a characteristic copulatory bursa The adults inhabit the upper small intestine of man They attach to the mucosa by means of the mouth parts and suck blood Each adult daily extracts about 0 5 ml of blood The adults migrate within the small intestine and each site of attachment persists temporarily as

Phylum	Class	*Disease*	*Causal agent*	*Stage and habitat in man*
Nemathelminthes	Class Nematoda	Hookworm	*Necator americanus*	Adults in intestine
			Ancylostoma duodenale	Adults in intestine
		Creeping eruption	*Ancylostoma braziliense*	Larvae in skin
			Uncinaria stenocephala	Larvae in skin
		Strongyloidiasis	*Strongyloides stercoralis*	Adults in intestine
		Trichostrongyliasis	*Trichostrongylus* spp	Adults in intestine
		Ascariasis	*Ascaris lumbricoides*	Adults in intestine
		Trichuriasis	*Trichuris trichiura*	Adults in intestine
		Enterobiasis	*Enterobius vermicularis*	Adults in intestine
		Trichinosis	*Trichinella spiralis*	Early Adults in intestine Late Larvae in muscles
		Filariasis bancrofti	*Wuchereria bancrofti*	Adults in lymphatics Larvae in blood
		Filariasis malayi	*Wuchereria malayi*	Adults in lymphatics Larvae in blood
		Onchocerciasis	*Onchocerca volvulus*	Adults and larvae in skin subcutaneous and other tissues
		Loiasis	*Loa loa*	Adults migrate in subcutaneous tissues larvae *in blood*
		Dracunculiasis	*Dracunculus medinensis*	Adults in skin and subcutaneous tissue
Platyhelminthes	Class Trematoda	Schistosomiasis mansoni	*Schistosoma mansoni*	Adults in portal and intestinal veins
		Schistosomiasis japonica	*Schistosoma japonicum*	Adults in portal and intestinal veins
		Schistosomiasis haematobia	*Schistosoma haematobium*	Adults in veins of the urinary bladder
		Schistosome dermatitis	Nonhuman schistosomes	Larvae in skin
		Fascioliasis	*Fasciola hepatica*	Adults in bile ducts
		Clonorchiasis	*Clonorchis sinensis*	Adults in bile ducts
		Opisthorchiasis	*Opisthorchis felineus*	Adults in bile and pancreatic ducts
		Paragonimiasis	*Paragonimus westermani*	Adults in lungs
		Fasciolopsiasis	*Fasciolopsis buski*	Adults in intestine
	Class Cestoda	Diphyllobothriasis	*Diphyllobothrium latum*	Adults in intestine
		Taeniasis saginata	*Taenia saginata*	*Adults in intestine*
		Taeniasis solium	*Taenia solium*	Adults in intestine occasionally cysticerci in tissues
		Echinococciasis	*Echinococcus granulosus*	Larval form in liver lungs and other organs
		Hymenolepiasis	*Hymenolepis nana*	Adults in intestine
		Dipylidiasis	*Dipylidium caninum*	*Adults in intestine*
		Sparganosis	Migrating larvae of *Diphyllobothrium* spp	Larvae in subcutaneous tissues

tions are more often severe The immunologic basis for these differences can only be inferred from experimental studies What is apparent is the greater significance which a positive laboratory finding (a helminth at some stage of its life cycle) has in relation to clinical findings in initially exposed individuals In reference to clinical findings per se in few of these diseases are they such as to lead to a specific diagnosis By themselves the clinical findings may suggest a presumptive diagnosis but the definitive diagnosis must invariably be made in the laboratory However even with a positive report from the laboratory the clinician must be cautious in evaluating the role of the parasite in the clinical picture presented For example the presence of hookworm eggs in the feces does not make the diagnosis hookworm disease A distinction must be made between asymptomatic infection and symptomatic infection or disease Nor does a negative direct stool examination rule out disease caused by blood or intestinal helminths When direct microscopic examinations of selected portions of entire stool specimens are negative appropriate concentration methods should be applied Only after thorough laboratory study occasionally requiring the examination of material obtained by proctoscope as in suspected schistosomiasis or duodenal drainage in suspected *Fasciola hepatica* or *Clonorchis sinensis* infection may a final decision be possible The proper investigation of suspected helminthic infections requires of the clinician a general knowledge not only of clinical manifestations but also of epidemiology helminthic life cycles and laboratory procedures

Brief mention should be made of the manner in which helminthic infection

sult from institution of a balanced high protein diet and in the treatment of severe infection it is essential that the utmost improvement from proper diet be attained before drug therapy is begun

Asymptomatic infection or the carrier state is common in endemic areas where asymptomatic outnumber symptomatic infections considering all age groups 20 to 40 times The worm burden is small and in these areas the carrier state is probably indicative of some degree of acquired host resistance

Laboratory Findings In symptomatic infection hookworm eggs are usually numerous enough to be detected by microscopic examination of a direct fecal smear It must be borne in mind that abdominal symptoms and pulmonary symptoms appear before eggs are discharged although a presumptive diagnosis may be made on the basis of the clinical history and the eosinophilic leukocytosis

The feces seldom contain gross blood in hookworm disease although usually positive for occult blood Charcot Leyden crystals are found in the feces in one half to two-thirds of the cases

Trichostrongylus eggs must be distinguished from hookworm eggs The former are larger and in a later stage of maturation when observed in a fresh fecal specimen

Generally the leukocyte count is normal or slightly elevated and the percentage of eosinophils increased to 15 or 30 per cent However in some early cases the leukocytosis may be marked and the eosinophil percentage as high as 70 or 80 per cent In such cases a diagnosis of eosinophilic leukemia has been entertained In general the more marked the anemia the lower the percentage of eosinophils The anemia is characteristically of the hypochromic microcytic variety

Differential Diagnosis Since hookworm disease occurs in areas in which beriberi and malaria in their cachectic forms are also more common these diseases must be differentiated from hookworm disease or their coexistence established

Treatment Specific therapy for the infection and that directed toward improvement of the nutrition and anemia should be considered simultaneously In the usual case with slight to moderate anemia anthelmintics can be administered followed by iron therapy (ferrous gluconate or ferrous sulfate) and a high protein balanced diet The current drug of choice is tetrachlorethylene although hexylresorcinol carbon tetrachloride and oil of chenopodium are useful under particular circumstances Tetrachlorethylene in hard gelatin capsules is given as a single dose oral treatment 3 ml being the dose for adults For children 0 2 ml is given for each year of age The night before treatment is to be given the patient is permitted a light fat free meal The following morning breakfast is omitted and the drug administered No food is permitted for 4 hr no alcohol for 24 hr Sodium sulfate (30 Gm in a glass of water) is given 4 hr after the tetrachlorethylene Ascariasis however if also present must be treated first with piperazine citrate (Antepar) hexylresorcinol or Hetrazan since tetrachlorethylene increases the activity of the ascarids Hexylresorcinol particularly when given in several courses of treatment as for ascariasis may simultaneously control concomitant ascarid and hookworm infections making other treatment unnecessary Piperazine citrate which is effective in ascariasis is not effective in hookworm infection

Carbon tetrachloride and oil of chenopodium are no more effective and are more toxic to the host than tetrachlorethylene and hexylresorcinol However they are less expensive and simpler to administer since they are given in liquid form thus making them useful for mass treatment

The aim in treatment is reduction of the worm burden to an asymptomatic level Eradication is difficult particularly in *Ancylostoma* infection

When anemia is severe and malnutrition with anasarca are also present blood transfusions and a high protein balanced diet should be given before drug treatment is begun In such cases the blood should be given in small increments and in a total amount sufficient to raise the hemoglobin level to 9 to 10 Gm per 100 ml In advanced cases it may be necessary to delay drug treatment for 2 to 3 weeks

Prognosis Generally the immediate prognosis is good When opportunity for reinfection persists and nutrition cannot be maintained a state of chronic debility develops In children development is impaired and in adults intercurrent disease proves serious

Prevention Many of the measures required are obvious but difficult to apply on a large scale Even if facilities for proper disposal of feces are provided it is no simple matter to educate the population in their use Soil pollution must be eliminated and until this is accomplished avoidance of direct skin contact with the soil (as by wearing of shoes) should be encouraged Periodic mass treatment of the population has been used in some hookworm control programs

CREEPING ERUPTION (Cutaneous Larva Migrans)

Definition Creeping eruption is an infection of the skin in man caused by the larvae of the dog and cat hookworm *A braziliense* The other dog hookworms *A caninum* and *Uncinaria stenocephala* and the horse botfly *Gasterophilus* in

a bleeding point Following fertilization the female liberates eggs which measure about 40 by 60 μ and are usually in the two to four celled stage when discharged in the feces

Necator americanus the "New World hook worm has a buccal capsule containing dorsal and ventral plates rather than teeth

The life cycles of these hookworms are similar Following development to the filariform or infective stage the larvae are capable of penetrating the skin to enter vessels which carry them to the lungs The larvae leave the alveolar capillaries and enter the alveoli They ascend the respiratory tree enter the pharynx and are swallowed They reach the intestine about 1 week after penetration of the skin and 3 or 4 weeks later are mature The adults have been known to survive in the human intestine for 5 years

Epidemiology Environmental conditions conducive to the development of the hookworm egg into the infective filariform larval stage are found in tropical and semitropical regions in which adequate rainfall occurs Given the appropriate environmental conditions hookworm infection will occur where there is opportunity for contact of the skin with contaminated soil Infection can be acquired by ingestion of filariform larvae but this mode of transmission is of little importance That development of hookworm eggs into the filariform larval stage can occur in contaminated bedclothes has been shown and also that fomites borne hookworm infection may be of importance

The white race is more susceptible to symptomatic infection than the Negro the latter still constituting however an important reservoir of infection Probably because of greater exposure males show a higher incidence of infection than females

Regarding the relative importance of the two hookworms it has been stated that "*Ancylostoma* presents a greater public health problem than *Necator americanus* the species now established in the southern United States because it is more harmful to the host is less amenable to treatment and its free living stages are more resistant to climatic conditions" (McCoy)

Pathogenesis and Clinical Manifestations The nature and severity of the clinical manifestations are determined by the stage and intensity of the infection During the invasion of the exposed skin by the larvae the affected parts become erythematous and edematous and there is severe pruritus These manifestations are more marked in *N americanus* infection than in *A duodenale* infection The lesions are commonest about the feet particularly between the toes and have been termed ground itch"

During passage of the larvae through the lungs cough and in severe infections fever are observed The pulmonary symptoms were particularly troublesome to soldiers engaged in close combat in the Asiatic campaign in the Second World War

Epigastric pain abdominal tenderness and occasionally vomiting and diarrhea can be prominent symptoms during the establishment and migration of the hookworms in the small intestine Roentgenographic studies at this stage may reveal a "cog wheel pattern of the upper small intestine presumably produced by the mucosal involvement As hookworm disease was observed in American troops in northern India and Burma where *A duodenale* infection predominates it was during this phase of the disease that medical aid was sought Eosinophilic leukocytosis was present but anemia was not nor did it develop presumably because of the short duration of the infection and early treatment Judging from the number of adult hookworms collected from posttreatment fecal specimens these were relatively light infections They were predominantly *A duodenale* infections which are generally accepted as being more severe than those caused by *N americanus* Clinical observations on induced *A duodenale* infections have been reported by Brumpt

The clinical picture which has been described as classic occurs in residents of endemic areas and differs from the above in that anemia with symptoms and visceral changes incident to the anemia are dominant The severity of the disease and the prognosis are dependent upon such factors as the age of the patient the magnitude of the worm burden the duration of the disease and diet Young children more often manifest the extreme anemia with cardiac insufficiency and anasarca The anemia usually develops slowly and results from loss of blood—that which the hookworm sucks and ingests and that which oozes into the intestinal lumen after the hookworm has left the site of mucosal attachment Patients may have a depraved appetite with a desire to eat coarse or gritty materials Those who survive to puberty show a retarded physical mental and sexual development Milder degrees of the disease as seen in older children and adults are characterized by lassitude dyspnea palpitation tachycardia and constipation in addition to the pallor of the skin and mucous membranes In most areas in which hookworm disease is common dietary deficiencies are also common Poor diet influences unfavorably the course of hookworm disease Study of hookworm infection in the dog has shown that host control of infection depends largely upon the development of immunity and that immunity does not develop or may be lost in the presence of malnutrition avitaminosis and anemia In man considerable clinical improvement can re

myocardium lungs trachea liver and gallbladder in addition to the intestine In other fatal cases intestinal perforation and peritonitis have been encountered

Laboratory Findings Although the nature of the clinical findings may be suggestive the definitive diagnosis must be made in the laboratory Fresh fecal specimens should be examined to avoid confusion with hookworm infection generally fresh specimens contain larvae in strongyloidiasis infections while in hookworm infection they contain eggs When pulmonary involvement is present the sputum should be examined for larvae Microscopic examination of the duodenal washings may readily establish the diagnosis It should be performed when other studies are negative and in determining the efficacy of treatment

Eosinophilic leukocytosis is common except in very severe cases in which eosinophilic leukocytes may be entirely absent

Treatment Gentian violet administered orally continues to be the most satisfactory treatment although it is only moderately effective It is given in capsules (1½ hr coating) with meals 0 06 Gm t.i.d for 10 to 14 days Nausea occasionally with vomiting and diarrhea may appear during the course of treatment Such manifestations may make it necessary to discontinue oral treatment When the oral route of administration cannot be tolerated or when it proves ineffective and further treatment is indicated gentian violet may be given by duodenal tube (25 ml of 1 per cent solution) For severe hyperinfective cases gentian violet has been given intravenously (25 ml of 0 5 per cent solution) Careful and prolonged posttreatment laboratory study is necessary to determine effectiveness of the drug in each case

Initial results with Nilodin (lucanthone hydrochloride) which is a thioxanthone derivative have been encouraging enough to merit further evaluation

Prognosis In the usual case the prognosis is good Since the occurrence of hyperinfection is unpredictable every effort should be made to eradicate the infection in each case In severe cases with hyperinfection the prognosis is poor

Prevention In general the measures are those for the control of hookworm infection In addition it is well to remember that infection may be contracted by ingestion of contaminated food (especially uncooked vegetables) or of contaminated drinking water and by contact

ASCARIASIS

Definition Ascariasis is an infection of man caused by *Ascaris lumbricoides* and characterized by an early transient pulmonary phase related to larval migration and a later prolonged phase during which the adult ascarids inhabit the lumen of the intestine

Etiology The adult ascarids are large (20 to 40 cm in length) and cylindric in shape with each extremity tapering to a blunt point Their usual habitat is the small intestine but they are prone to migration The eggs are elliptic (30 to 40 μ by 50 to 60 μ) and have an irregular dense outer shell and a regular translucent inner shell They are not infective upon discharge from the body Under proper conditions of warmth and moisture the ovum develops to the infective larval stage in about 4 to 5 weeks Upon ingestion of the egg at this stage the larva is liberated in the small intestine It migrates through the wall and ultimately reaches the lungs After about 10 days in the pulmonary capillaries and alveoli the larvae pass in turn to the bronchioles bronchi trachea and epiglottis are swallowed and develop into male and female adults in the small intestine

Epidemiology and Distribution Infection follows the ingestion of the embryonated egg contained in contaminated food or more commonly the introduction of the eggs into the mouth by the hands after contact with contaminated soil Since the eggs are resistant to desiccation and wide variations in temperature the disease has a world wide distribution

Pathogenesis and Clinical Manifestations Because of the extensive migration of which both the larvae and adults are capable clinical manifestations may be unusually diverse In heavy infections severe bronchopneumonia occasionally fatal in children can occur during the migration of the larvae through the lungs Light infections assume importance when single or several adult ascarids obstruct the appendix the bile the pancreatic ducts or other hollow structures of the upper intestinal or respiratory tracts

Laboratory Findings The diagnosis is usually made by finding the ova in the feces The intact ova are characteristic and not easily confused with other ova

Symptomatic infection especially during the phase of larval migration through the lung is usually accompanied by fever and eosinophilic leukocytosis

Treatment Only symptomatic treatment can be used during the period of pulmonary involvement by the migrating larvae For removal of the adult worms from the intestines piperazine citrate as a flavored syrup administered in a single dose after breakfast on two successive days will cure 94 per cent of cases (Brown) For younger children (30 to 50 lb) 2 Gm piperazine equivalent contained

their larval stage may produce a similar cutaneous infection

Etiology The adult stage of *A brasiliense* occurs regularly only in the dog and cat The larvae emerging from eggs discharged in the feces develop to the filariform stage and then are capable of penetrating the skin In man the larvae usually remain in the skin and migrate producing an irregular erythematous tunnel visible on the skin surface

Epidemiology and Distribution Dogs and cats constitute the reservoir of infection for man Transmission among animals and to man requires environmental temperature and humidity appropriate for development of the egg to the infective filariform larva stage Such conditions are found in the southeastern United States coastal areas of Central America northern South America northern and southern Africa and some areas of the Far East Beaches and other moist sandy areas are hazardous because animals choose such areas for defecation and the *A brasiliense* eggs develop well in such soil

Pathogenesis and Clinical Manifestations The site of penetration of the skin by the larva becomes apparent in a few hours The hands feet and legs are most frequently involved The migration of the larva in the skin is accompanied by severe itching Scratching may lead to bacterial infection In the course of one week the initial red papule develops into an irregular erythematous linear lesion which may attain a length of 15 to 20 cm Development of *A brasiliense* to the adult stage occurs rarely in man

Wright and Gold have observed Loeffler's syndrome in 26 of 52 cases of creeping eruption Transient migratory pulmonary infiltrations were associated with an increase in eosinophils in the blood and sputum The lesions have been interpreted as an allergic reaction to the helminthic infection

Laboratory Findings Eosinophils occur in the lesion but eosinophilic leukocytosis is slight except when Loeffler's syndrome appears The percentage of eosinophils in the blood may then rise to 51 per cent and in the sputum to 90 per cent

Treatment Carbon dioxide snow or ethyl chloride spray may be applied locally to destroy the larva Superficial bacterial infections are improved by wet dressings and elevation of the extremity

Prognosis Untreated infections may last several months Treatment is usually sought because of severe pruritus and moderate incapacitation The above treatment is usually successful

Prevention Dogs and cats should be prevented from contaminating recreation areas Contact of the skin with the soil should be avoided in areas suspected of being contaminated

STRONGYLOIDIASIS

Definition Strongyloidiasis is an intestinal infection of man and other higher mammals caused by *Strongyloides stercoralis*

Etiology The adult female resides in the mucosa of the upper small intestine The embryonated eggs soon develop into the rhabditiform larvae in which form they are observed in the feces Further larval development may take one of several courses (1) In a suitable external environment the indirect or sexual cycle occurs (2) Under less suitable external circumstances the rhabditiform larvae develop into the infective filariform stage (direct or asexual cycle) (3) Development to the infective stage is presumed to occur as well in the lower intestine the filariform larvae then entering the body through the skin of the perineum or through the intestinal wall Mechanisms such as those mentioned in (3) above may explain the long periods of infection observed (20 to 30 years) in those who have left endemic areas

The course of the filariform larvae of *S stercoralis* after entering the skin the oral mucosa or the intestinal mucosa resembles that of the hookworm larvae In the intestine the females burrow into the mucosa from which site embryonated eggs are discharged

Epidemiology and Distribution The usual mode of infection is the penetration of the skin by larvae present in contaminated soil Some infections may result from ingestion of contaminated food and drink and some are believed to be transmitted by contact

Endemic areas are found primarily in the tropics although sporadic cases have appeared in temperate regions

Pathogenesis and Clinical Manifestations Erythema with petechiae and pruritis characterizes the site of cutaneous penetration by the larvae Cough occasionally with dyspnea and hemoptysis accompanies the stage of migration through the lungs X rays may exhibit pulmonary infiltration at this stage

Epigastric pain and tenderness nausea flatulence and vomiting as well as diarrhea alternating with constipation may be observed during the intestinal phase of development The diarrhea may persist for long periods causing excessive loss of fluid Intestinal ulceration and sloughing are noted in severe cases As with hookworm infection many asymptomatic infections occur and most symptomatic infections occasion only vague complaints

In massive infection there may be serious complications The extensive involvement possible is illustrated by the fatal case described by Kyle et al in which extensive pulmonary hemorrhage and edema were observed Larvae were found in the

as 97 per cent of cases when prescribed in a single course of 7 days It is given in syrup form each day before breakfast with total daily dose of 250 mg for children weighing up to 15 lb 500 mg for those weighing between 16 and 30 lb 1 Gm for those between 31 and 60 lb and 2 Gm for those over 60 lb (Brown) When renal insufficiency is present the piperazine should be given in smaller dosage to avoid neurotoxicity

Prognosis The prognosis with reference to the duration of infection is good particularly when the other measures mentioned are carried out in addition to drug treatment

Prevention Methods of preventing autoinfection and dissemination within a group involving children are difficult to apply Personal and environmental hygiene should be stressed and anthelmintic and symptomatic treatment of pruritus are instituted To control infection within a group simultaneous treatment of all cases must be carried out

TRICHURIASIS

Definition Trichuriasis (whipworm infection trichocephaliasis) is an intestinal infection of man caused by *Trichuris trichiura* and is characterized by invasion of the colonic mucosa by the adult *Trichuris*

Etiology The adult whipworms possess a thread like anterior two thirds and a stouter posterior third giving them a whiplike structure The eggs are characteristic being barrel shaped brown and translucent and having knoblike extremities

Epidemiology The mode of spread resembles that of ascariasis the eggs generally being introduced into the mouth by contaminated fingers

Pathogenesis and Clinical Manifestations Symptomatic infection generally requires the presence of large numbers of adult whipworms and may be correlated in part with the degree of mucosal involvement Heavy infections usually occur only in children and may be accompanied by nausea abdominal pain and diarrhea

Laboratory Findings In symptomatic infection large numbers of eggs are present in the feces Eosinophilic leukocytosis and anemia may accompany such infections

Treatment The most readily available and least toxic drug although not highly efficient is hexylresorcinol The evening before the drug is to be administered the meal should be light and breakfast should be omitted In the morning hexylresorcinol is given orally in hard gelatin capsules the dose for children being 0 1 Gm for each year up to the age of ten and for older children and adults 1 Gm The hexylresorcinol capsules are swallowed without chewing since hexylresorcinol is irritating to mucosal surfaces A saline purge e g sodium sulfate is given 2 to 3 hr after administration of the drug and no food eaten for 4 to 6 hr This procedure should be repeated in 4 to 5 days If the worm burden has been appreciably reduced no further treatment is necessary

When involvement of the colon is extensive as judged by the clinical symptoms and/or the worm burden hexylresorcinol should be given as an initial treatment in the form of a retention enema (one half to one liter hexylresorcinol in 0 1 per cent aqueous solution) Petroleum jelly is applied to the perineum to prevent cutaneous irritation by the hexylresorcinol

If heavy infection persists piperazine citrate as recommended for enterobiasis may be used

Prognosis In uncomplicated *Trichuris* infection the prognosis is good Symptomatic infection can be controlled with the drugs mentioned although eradication of the infection is difficult

Prevention Measures recommended for ascariasis apply also to trichuriasis

TRICHOSTRONGYLIASIS

Definition Trichostrongyliasis is an intestinal infection of man and other mammalian hosts including sheep goats and cattle

Etiology Almost a dozen species of *Trichostrongylus* are known to have infected man Few human infections have been reported in the United States In view of the high frequency of animal infections here the low incidence of human infections is difficult to understand The possibility exists that some may be diagnosed as hookworm infection

The ova resemble those of the hookworm but are larger and when observed in a fresh fecal specimen show a more advanced stage of segmentation (16 to 32 celled stage)

Pathogenesis Infection is acquired by ingestion of the larvae rather than by their penetration of the skin The adult maintains residence in the intestine for long periods Sandground who infected himself observed infection to last more than 8 years

Manifestations Diarrhea is observed occasionally when infection is massive but most infections are asymptomatic The parasite owes its importance primarily to the resemblance of its ova to those of the hookworms Moreover because the trichostrongylidae do not respond to anthelmintics effective in hookworm infection it may be assumed incorrectly that one is dealing with refractory hookworm infection

Laboratory Diagnosis The diagnosis depends upon the finding of the ova in the feces Since they are few in number they are usually found only when a concentration method is used In symp

in 20 ml syrup constitutes each dose for older children and adults 3 to 3 5 Gm is given No particular dietary regulation is necessary The drug *must be administered with caution when renal* insufficiency is present since impaired elimination may produce neurotoxic signs

Prognosis The prognosis in intestinal infection is generally good When acute or chronic obstruction of ducts or hollow viscera has occurred the im mediate prognosis is determined by the promptness in diagnosis and treatment

Prevention Ascariasis is primarily a household infection of rural areas All infections should be treated personal hygiene stressed and adequate toilet facilities provided

VISCERAL LARVA MIGRANS

This is a clinical syndrome usually observed in children and characterized by hepatosplenomegaly skin rash and recurrent pneumonitis with respira tory distress in the form of wheezing There is generally a history of dirt eating and contact with dogs or cats in or near the household Ocular in volvement and central nervous disturbances in the form of convulsions may also be observed

Leukocytosis with eosinophilia to high levels (over 60 per cent) and hypergammaglobulinemia are common The eosinophilic leukocytes are un usual in that they are large and have vacuolated cytoplasm containing granules which vary in size and are present in smaller than normal numbers

This syndrome with various degrees of clinical severity follows the ingestion of the infective eggs of nematodes whose life cycle is not completed in man It is caused most often by nematodes whose life cycle is completed in the dog (*Toxocara canis*) or in the cat (*Toxocara cati*) Larvae of the *Toxo cara* become widely disseminated in the body and incite a granulomatous reaction Lesions are promi nent in the liver lungs skeletal muscle and brain Larvae with eosinophilic leukocytic and granulo matous reactions have been noted in liver biopsies

The clinical diagnosis may be made on the basis of the findings described Immunologic tests are helpful but at this time do not have sufficient speci *ficity to be diagnostic Visceral larva migrans is an* other variety of helminthic infection capable of causing Loeffler s syndrome When the respiratory *difficulty is pronounced ACTH or adrenal cortical* steroids may prove helpful There is no particular treatment for the other lesions

In control measures are directed toward pre *venting* ingestion of the *Toxocara* eggs Removal or repeated treatment of infected cats and dogs must be considered as well as modifying the diet to reduce the temptation to ingest contaminated ma *terials*

ENTEROBIASIS

Definition Enterobiasis (pinworm seatworm or threadworm infection oxyuriasis) is an intestinal infection of man caused by *Enterobius vermicularis* and characterized by perianal pruritus

Etiology The adults are small fusiform worms usually inhabiting the cecum and colon attached to the mucosa The female averages 10 mm in length the male 3 mm The eggs are deposited by the female on the perineal skin the migration gen *erally occurring at night Each egg contains an em* bryo which a few hours after being deposited develops into the infective larva After ingestion of the egg the larva is released in the small intestine *The adult stage* is soon reached and in *less than* 1 month from the time of ingestion newly devel oped gravid females are again discharging eggs They are planoconvex and measure approximately 20 by 50 μ The shell is clear and doubly contoured

Epidemiology and Distribution The eggs usu ally reach the mouth of the human host by way of contaminated hands food or drink although air borne transmission may also occur They are relatively resistant to desiccation and because they are infective soon after discharge from the body transmission within family and children s groups occurs readily Enterobiasis is found in all climates and is probably the commonest helminthic infection of man Its low incidence in some tropical areas however defies explanation

Clinical Manifestations The commonest symp tom is pruritus ani which is most troublesome at night being related to the migration of the gravid female worms Scratching may lead to perineal eczema or pyogenic infection

Laboratory Findings Examination of material obtained from the perineal skin for ova by means of a cellophane or Scotch tape swab is essential for the detection of enterobiasis Less than 5 per cent of infections are diagnosed by searching for ova in the feces Scrapings from under the nails may *reveal ova The diagnosis* can be made by exam ining the feces for adult worms following a laxa tive or an enema Eosinophilic leukocytosis is in constant

Treatment All infected individuals in an affected *communal group should* be treated simultaneously The aim in drug treatment is reduction of the worm burden Drug treatment combined with such meas *ures as* (1) providing a sleeping garment which prevents contamination of the fingers with ova from the perianal region (2) instituting a morning shower (3) lukewarm water enemas and (4) local antipruritic ointments is directed toward producing asymptomatic infection with eradication or cure not the immediate objective

The preferred therapeutic agent is piperazine citrate which has been found effective in as high

other parts of the world In the United States where the incidence is between 15 and 20 per cent there is "more than three times as much trichinosis as is known in all of the rest of the world put together" Studies show that this high incidence has continued The ratio of asymptomatic to symptomatic infection is high

Pathogenesis and Clinical Manifestations The course and symptomatology vary remarkably The clinical diagnosis in the sporadic case may be difficult Diarrhea is an early manifestation related to the development of the adults in the intestinal mucosa and is observed in about half of the cases It usually appears within 24 hr after ingestion of the uncooked or undercooked meat containing the encysted larvae The next stage that of muscular invasion begins about the end of the first week and may last for as long as 6 weeks Most of the clinical manifestations are related to the invasion and encystment of the larvae in skeletal muscles A myositis is produced with basophilic granular degeneration of the invaded muscle fiber Adjacent fibers exhibit hyaline or hydropic degeneration and the focus becomes infiltrated with neutrophilic and eosinophilic leukocytes some lymphocytes and mononuclear macrophages Hyperemia edema and hemorrhages are constant features

Larvae do not encyst in cardiac muscle nor can they be found readily there Despite this an intense myocarditis has been observed and may be of significance in fatal cases

Larvae have been observed in association with less severe focal lesions in the lungs and brain and in other viscera with no associated inflammatory reaction

The significant clinical manifestations are noted during the period of migration and muscle invasion Fever is probably the commonest manifestation Ocular manifestations may be among the most striking The edema of the eyelids often accompanied by conjunctivitis and chemosis is difficult to explain but may be related to larval invasion of the eye muscles and possibly other retrobulbar tissues Also a constant manifestation is the muscular pain and tenderness Electromyograms have disclosed extensive fibrillation Manifestations in the skin and appendages include (1) a maculopapular rash which usually lasts for several days and (2) subungual "splinter hemorrhages"

Laboratory Findings The most constant finding and one of significance early in the course of the disease is the eosinophilic leukocytosis (over 500 eosinophilic leukocytes per cubic millimeter) It appears generally before the end of the second week and rises In cases of moderate severity the percentage of eosinophilic leukocytes ranges between 15 and 50 per cent In severe cases particularly ter



FIG 150 *Trichinella spiralis* Larva encysting within a skeletal muscle fiber At this stage myositis and edema have partially subsided (×135)

minally the eosinophilic leukocytes may disappear entirely

The skin test becomes positive early in the third week of infection The antigen is prepared from larvae and used in a dilution of about 1 10 000 One one hundredth of a milliliter is injected intradermally and immediate and delayed reactions looked for The usual positive response is immediate a wheal of 5 mm or more appearing within 30 min Nonspecific reactions may be related to the ingestion of meat containing nonviable trichinae

The precipitin reaction becomes positive after the third week Its value in diagnosis is increased if the reaction is initially negative and becomes positive or if the titer rises during the course of the disease It remains positive for about a year

In attempting to arrive at a definitive diagnosis examination of the feces for the adult worms is of little help Examination of the blood cerebrospinal fluid or muscle biopsy is more rewarding Microscopic study of laked venous capillary or arterial blood is the simplest test which may make a definitive diagnosis possible Larvae have been found in the peripheral blood as early as the fifth day in experimental infections Larvae may be present in the cerebrospinal fluid in the absence of clinical central nervous system involvement Biopsied muscle is best studied by use of a compressor which permits examination of the entire specimen Maceration and digestion methods are used in survey

tomatic infections there may be leukocytosis with marked eosinophilia (e g 80 per cent)

Treatment Piperazine citrate as recommended for enterobiasis has given good results

Prevention Contamination of the hands and food grown in contaminated soil are to be avoided

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199 TRICHINOSIS

Gustave J Dammin

Definition Trichinosis is caused by the intestinal nematode *Trichinella spiralis* As a clinical infection it is characterized by diarrhea during the development of the adults in the intestine and by myositis *with systemic reaction during the larval migration* and invasion of the skeletal muscles

Etiology and Epidemiology Infection is contracted following ingestion of meat containing the encysted larvae of *T spiralis* There are no intermediate hosts both the adult and larval stages developing in the same host *Trichinella spiralis* exhibits little host specificity infection having been *produced or observed in the bear wild boar* horse cow dog cat rabbit guinea pig mouse and marine mammals in addition to the rat and the pig Man is particularly susceptible most fowl are resistant Among pigs infection is contracted following feeding of uncooked pork scraps less often by eating infected rats Rats also feed on uncooked pork scraps and in addition maintain a high inci*dence of infection by their cannibalism*

Soon after liberation of the larvae from their cysts they migrate into the mucosa and within a week the viviparous female is discharging *larvae* (100 by 6 μ) which enter vascular channels and are distributed throughout the body Larviposition continues for about 4 to 6 weeks The larvae enter skeletal muscle and encyst (Fig 150) The muscles of the diaphragm tongue and eye the deltoid pectoral and intercostal muscles are most often affected Larvae carried to sites other than skeletal *muscles do not encyst but disintegrate* The life cycle can be carried further only if a new host ingests the encysted larvae

Geographic Distribution Trichinosis is common in Europe and North America and uncommon in

periodic in W bancrofti infections peak concentrations being between 9 P M and 2 A M Wuchereria malayi is similarly but less regularly periodic In many western Pacific islands including Samoa and Fiji W bancrofti is nonperiodic the reason for this is entirely unknown The danger of infection in the periodic disease is nocturnal but the non periodic form is often transmitted by sylvan mosquitoes in natural cover during the day

Wuchereria bancrofti infection is endemic between latitudes 41 N and 30 S Distribution is irregular and there are many peculiar skip areas" in this geographic pattern presumably because the endemic disease can be maintained only where human infection and mosquitoes are prevalent *Wuchereria malaya* infection is confined to the Far East including India Malaya East China and the Philippines There were approximately fifteen thousand *W bancrofti* infections among American military personnel in the Second World War (Wartman)

A small endemic focus of *W bancrofti* once existed near Charleston S C but no new cases have been observed in several years

Pathogenesis As larvae migrate to the lymphatics they produce irritation whether by some secretion or entirely by hypersensitivity responses of the host being unknown The larvae reach maturity in lymph nodes and incite hypertrophy granulomatous inflammation and obstruction often with retrograde lymphangitis Repetition of this process for many years can lead to permanent blockage scarring and elephantiasis Secondary bacterial infection is thought by some to be important in the etiology of elephantiasis but this has not been established Elephantiasis is actually a relatively unusual complication of filarial infections If repeated reinfections do not occur the disease is self limited

Manifestations Acute filariasis manifests itself as a series of brief attacks over a period of weeks Symptoms vary greatly in severity and include headache fatigability vertigo photophobia and muscle pain Fever is low grade and chills are rare in the early stages Examination shows lymphadenopathy streaks of lymphadenitis and sometimes circumscribed reddish swellings of the extremities The male genitalia are frequently involved with epididymitis orchitis hydrocele or scrotal edema Conjunctivitis is common pleural friction rubs have been described Urticaria is rare Such an attack frequently referred to by the Samoan term *mumu* ordinarily subsides in 12 to 24 hr but recurrences are common particularly after strenuous exercise Secondary bacterial infection has been found to play no part in these acute episodes nor is mechanical blockage of lymphatics by the worms responsible for the swellings It is probable that hypersensitivity to the parasite or its products is the underlying mechanism of *mumu* but conclusive evidence on this point is lacking

With repeated exposures infected individuals show palpable thickening of lymphatic channels (often first noted in the spermatic cords) rubbery adenopathy and in a small percentage of cases elephantiasis develops this complication is rare below the age of twenty even in natives of heavily infested areas The chronic stage of the disease is often punctuated by acute bouts of "filarial fever" with chills fever headache tender lymphadenopathy localized areas of erythema and edema and severe muscle pain These are thought to be hypersensitivity reactions induced by release of filarial antigen when adults or microfilariae die or a new infection occurs This concept is supported by the frequent occurrence of filarial fever after institution of chemotherapy and by the fact that an attack can sometimes be produced by intracutaneous injection of the specific antigen in skin testing

Laboratory Findings Eosinophilia accompanies *mumu* in about two thirds of the cases and is also common during attacks of filarial fever in the later stages of the disease Although adult worms are often demonstrable in biopsied lymph nodes this procedure is not often used and excision of nodes often induces a symptomatic flare up of the disease Complement fixation and skin tests are available but neither is reliable in the individual case Diagnosis is best established by demonstration of microfilariae in Giemsa or Wright stains of peripheral blood Microfilariae are motile and can also be found in wet smears When the periodic form of the disease predominates specimens should be collected at night

Treatment The only agent effective against the adult worms is thiacetarsamide (Caparsolate sodium) which is given intravenously as a 1 per cent solution in a dosage of 1 0 mg per kg daily for 15 days Diarrhea sometimes accompanies administration of this drug Although microfilariae may be demonstrable in the blood after a course of thiacetarsamide they soon disappear and relapse is rare

Hetrazan (diethylcarbamazine) in an oral dosage of 2 0 mg per kg t i d for 3 or 4 weeks is an effective microfilaricide The initiation of treatment with this drug may be followed by a bout of filarial fever that usually subsides within 3 days

Antimony compounds no longer have a place in the treatment of filariasis

Other treatment is symptomatic Reassurance of the patient is very important in this disease Vaccines and antiserums are valueless Bandaging and surgery are sometimes beneficial in elephantiasis The prognosis for life is excellent particularly if

studies of diaphragms obtained at autopsy and for biopsy specimens as well

Differential Diagnosis Trichinosis must be distinguished from acute glomerulonephritis typhoid fever meningitis rheumatic fever rheumatoid arthritis eosinophilic leukemia dermatomyositis and periarteritis nodosa

Treatment There is as yet no specific treatment for trichinosis Symptomatic treatment is directed toward the relief of pain maintenance of an adequate caloric and fluid intake and assuring the patient of adequate sleep by use of sedatives ACTH is reported to have controlled the systemic reaction in severe infection and is recommended for such cases However in experimental infections cortisone administration results in more prolonged persistence of the adult worms in the intestine increased numbers of larvae in the musculature and partial suppression of the immune response

Piperazine citrate has been found effective in removing the adults from the intestine in experimental infections It would seem advisable to use piperazine citrate (as prescribed for enterobiasis) during the early phases when adult trichinae are suspected of being in the intestine This would apply when diarrhea and other abdominal symptoms have developed subsequent to the ingestion of undercooked meat and also later when fever and eosinophilia have appeared since treatment may reduce the period of larviposition and thereby shorten the clinical course

Prognosis The prognosis in children is usually better than in adults If there is no serious involvement of the myocardium or respiratory muscles the prognosis is generally good The longer the appearance of symptoms is delayed the better the prognosis Diarrhea early in the course is a favorable sign Analysis of larger series of sporadic and epidemic cases shows the mortality rate to be about 5 per cent

Prevention The responsibility for control rests with the consumer Adequate cooking of pork involves heating all portions of the meat to 55 C Freezing procedures to kill the larvae require a temperature of −15 C for 20 days or −18 C for 24 hr Proper smoking and pickling will also destroy the larvae Important in control is the cooking of garbage fed to hogs There is at present no practical method of inspection which will detect trichinous pork

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200 FILARIASIS

Ivan L Bennett Jr

Definition Filariasis is a group of disorders produced by infection with nematodes of the super family Filarioidea These worms invade the subcutaneous tissues and lymphatics of man producing reactions ranging from acute inflammation to chronic scarring The clinical pictures produced by different species in this group are more or less specific The term *filariasis* is commonly used to designate the disease produced by *Wuchereria bancrofti* or *W malayi* the organisms responsible for elephantiasis The disorders associated with infection by *Loa loa* or *Onchocerca volvulus* are usually referred to as *loiasis* and *onchocerciasis*

Filariasis (Wuchereriasis)

Etiology and Epidemiology Adult worms live only in the lymphatics of human beings the male measuring 35 mm and the female 50 to 100 mm Gravid females release microfilariae in large numbers into the lymph and blood These embryos develop further only if ingested by a proper mosquito vector usually *Culex fatigans* although many *Culex Aedes* and *Mansonia* species are good hosts After further development in the vector larvae migrate to the mouth parts and if inoculated into a human host reach maturity in about a year In the absence of reinfection man harbors microfilariae for 5 to 10 years the reproductive life of the adult worms The release of microfilariae into the blood is strikingly

it occurs in the Nile Delta Anglo Egyptian Sudan Zanzibar Madagascar and Central Africa

Schistosoma japonicum affects the population engaged in agriculture In Japan China and the Philippines men are more frequently infected than women An important source of infection in the Orient is the use of human excreta as a fertilizer in vegetable gardens

Schistosoma haematobium is distributed widely throughout the African continent and to a much less extent is found in Spain Portugal Cyprus and Greece In Africa it is highly prevalent among the indigent agricultural population of the Nile Valley

The best attack on schistosomiasis is preventive Public health measures including proper disposal of human excrement and anthelmintic therapy should be carried out in endemic areas Extermination of the mollusk intermediate host by chemical agents in areas where the infestation rate is high is mandatory Sodium pentachlorophenate has been tried against the snails *Australorbis glabratus* and *Oncomelania nosophora* with promising results

Another efficient molluscacide is 2 cyclohexyl 4 6 dinitrophenol

SCHISTOSOMIASIS MANSONI (Intestinal Bilharziasis Schistosomal Dysentery)

Etiology and Life Cycle The male worm measures about 1 cm in length and has a breadth of about 0 13 cm The female is long slender and cylindroid its average length being 1 4 cm and its breadth about 0 016 cm The male has a central trough the gynecophoral canal that enfolds the female during copulation The eggs are bluntly oval have a lateral spine and measure about 140 μ by about 60 μ They are passed in the feces rarely in the urine and can infect only the proper snail which serves as the intermediate host The ova must reach fresh water if the parasite s life cycle is to be completed As stated by Belding the life cycle includes the passing of the ova from the definitive host or man its hatching in water the liberation of a free swimming *miracidium* the penetration of a proper species of snail by the miracidium the metamorphosis of the larvae into *cercariae* (the infective form of the schistosome) their return to water the penetration of the skin of man and finally the migration and growth of the worms in the blood vessels of man and the laying of eggs by the female Adult worms live in the inferior and superior mesenteric veins and the hemorrhoidal plexus

Pathology According to E Koppisch schistosomiasis mansoni is divisible into three stages (1) an early stage of migration during which the cercariae are being carried by the blood to the liver maturing into adult parasites within intrahepatic portal veins (2) an intermediate stage during which ova are accumulating in various viscera and (3) a late stage characterized by serious and permanent damage to organs mainly through fibrosis

The greatest damage to man s tissues is caused by the eggs However the secretions metabolic products and toxins of the adult worms are believed by some to play an important role As long as they are living the adult parasites apparently produce no reaction but when they die numerous eosinophils gather about them

Histologically the predominant lesion is the pseudotubercle—a lesion incited by the ova retained in the tissues

In the colon ulceration is rare and the distal parts are more frequently and seriously involved Congestion of the mucosa punctate hemorrhages and thickening of the wall due to edema and fibrosis of the submucosa are the main findings In Egypt pedunculated or sessile polyps are commonly found in the rectum Changes in the liver are largely portal Ova transported from the colon by venous blood are retained in the portal spaces Pseudotubercles form around them accompanied by eosinophils Grossly the organ is enlarged during the intermediate stage but later contracts as scarring increases On section the characteristic feature is a periportal fibrosis The larger portal veins are surrounded by collars of fibrous tissue constituting the characteristic pipe stem cirrhosis of Symmers The spleen frequently becomes enlarged sometimes weighing more than 1 500 Gm Ova and pseudotubercles in the spleen are more frequently encountered in Egypt than in America In the lungs small grayish nodules averaging 1 mm in diameter are visible or palpable throughout the pulmonary tissue These are made up of pseudotubercles around the eggs that have been carried by the blood In some cases the gross appearance of the lung resembles miliary tuberculosis Microscopically there are pseudotubercles, patches of marked eosinophilic infiltration and occasionally hemorrhages The eggs arriving in the lungs as emboli obstruct the small arteries and the intima becomes thickened by fibrosis In time the right side of the heart undergoes hypertrophy and failure ensues

Manifestations The clinical manifestations of schistosomiasis may be correlated with anatomic changes resulting from the reaction of tissues to the parasites and their ova The finding of schistosome ova in the stools of apparently healthy individuals is a relatively frequent occurrence in endemic areas Unlike the bacterial infections the parasites do not multiply within the human host Thus the symptomatic disease is dependent upon the continued exposure to infection

Itching may or may not occur shortly after exposure and urticaria is variable Mild pyrexia may

infected individuals leave endemic areas or other wise avoid reinfections

Onchocerciasis

This infection is produced by *Onchocerca volvulus* and is transmitted by flies of the genus *Simulium* The disease is widespread in southern Mexico and Guatemala and is common in Central Africa The characteristic lesions of onchocerciasis are subcutaneous nodules that tend to occur in the region of the head although in Africa they are said to be common on the trunk The aspirated contents of the nodules contain adult worms and microfilariae

Treatment consists of surgical excision of the nodules and administration of Hetrazan Except for occasional invasion of the eye the disease has a favorable prognosis unless the number of nodules exceeds 50 in the individual patient

Loiasis

This form of filariasis is produced by *Loa loa* and is prevalent in West and Central Africa The infection is transmitted by flies of the genus *Chrysops* Localized areas of allergic inflammation in the subcutaneous tissues known as *Calabar swellings* are the hallmark of the disease although infestation may be completely asymptomatic The adult worms are sometimes visible beneath the conjunctiva and *Loa loa* is often called the *eye worm* Diagnosis can be made by finding the adult worm or demonstration of microfilariae in contents of Calabar swellings or in blood smears Treatment is symptomatic and the prognosis is good

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201 SCHISTOSOMIASIS (Bilharziasis)

Rafael Rodriguez Molina

Definition Schistosomiasis (bilharziasis) is a general term employed to describe a group of disease entities produced in man and animals by three closely related species of digenetic trematodes or blood flukes belonging to the family Schistosomatidae These worms are *Schistosoma mansoni* *S haematobium* and *S japonicum* They inhabit the circulatory system of man and animals living in tropical and subtropical countries The organs and tissues most frequently affected are the colon urinary bladder liver spleen rectum genitalia lungs mesentery and peritoneum

History Bilharz in 1851 first demonstrated the role of *S haematobium* in the prevailing hematuria and dysentery among the native population of Egypt The presence of two types of spined ova and of two clinical forms of the disease the vesical and the intestinal caused confusion until Sambon in 1907 demonstrated the existence of two species *S haematobium* and *S mansoni* The presence of schistosomiasis in Egyptian mummies indicates that it is an ancient disease It was in Puerto Rico in 1904 that the ova of *Schistosoma mansoni* were first discovered among the indigenous population of the Western Hemisphere by Gonzalez Martinez Katsurada in Japan in 1904 found the eggs in the stools of patients affected with Katayama disease Other Japanese investigators demonstrated that dogs cats horses cattle and wild rats were natural hosts or reservoirs of infection

Epidemiology and Control Schistosomiasis is probably the most important of the parasitic diseases affecting man not only because of the extensive pathologic changes produced by the parasites but also because of its world wide distribution and the number of individuals affected With the remarkable control of malaria during recent years the eradication and control of schistosomiasis has become a challenge to the public health officer the sanitary engineer the malacologist the zoologist and the physician

The continuing prevalence of schistosomiasis depends upon the disposal of human excrement into fresh water the presence of suitable snail hosts and the exposure of persons to water infested with cercariae Promiscuous defecation latrine drainage and unsanitary sewage disposal are the more important sources of pollution of streams and rivers The disease is contracted by persons washing clothes bathing wading or working in contaminated water

Schistosomiasis is more frequently encountered in rural than in urban communities and is associated with agricultural endeavors such as the irrigation of land It is more prevalent among low income groups

Of the three disease producing blood flukes of man *S mansoni* is by far the most common in the Western Hemisphere It was brought to the Caribbean area and South America by African slaves In South America Venezuela Dutch Guiana and Brazil are the areas in which it is present In Africa

perience has shown that for a period of about 1 month following administration of either Fuadin or Anthiomaline stool examination and rectal biopsy may give negative results which are misleading It is preferable to give several Fuadin courses (50 to 60 ml) a year if the tolerance of the patient per mits Toxic manifestations occur in 20 to 30 per cent of the patients Pain at the site of the injection and generalized arthralgia are common however hepa titis acute nephritis and thrombocytopenic purpura have been observed Triostam (sodium antimonyl gluconate) has been used with success It is well tolerated and toxic reactions are rare One disad vantage is that the drug must be administered intra venously In the late stages of the disease these therapeutic measures are palliative since the pa tient is suffering from cirrhosis of the liver portal hypertension or hypersplenism The indications for surgical procedures are the same as for the other forms of portal hypertension (p 1507)

Prognosis The prognosis is good in infections where the symptomatology is mainly secondary to colitis but when the liver spleen and lungs are involved the prognosis is poor

SCHISTOSOMIASIS JAPONICA (Eastern Schistosomiasis Katayama Disease)

Etiology and Life Cycle The male worm has an average length of about 1 5 cm and a breadth of 0 05 cm The female is long and slender averaging 1 9 cm in length and 0 03 in breadth The eggs are slightly oval and are shorter wider and distinctly smaller than those of the other two species meas uring about 90 by 70 μ Mature eggs have a minute hook or spine laterally situated and smaller than that of *S mansoni* The ova are passed in the feces only The life cycle is similar to that of *S mansoni* but various species of *Oncomelania* and *Katayama* snails are utilized as intermediate hosts *Schistosoma japonicum* lives in the inferior mesenteric venules but frequently migrates into the venules draining the large intestine and oviposits there

Pathology *Schistosoma japonicum* resembles the mansoni type but because of the much greater number of ova deposited by the female worms in the former disease the manifestations are frequently more severe Cirrhosis of the liver develops earlier and the duration of the disease is shorter—death often ensuing in 2 to 5 years In advanced cases the gross post mortem findings are emaciation and pallor large or contracted liver with periportal fibrosis splenomegaly with fibrosis of pulp ascites fibrotic nodules over the colonic peritoneum fibrous thickening and rigidity of the colon with small polyps projecting from the mucosa and thickening and fibrosis of the omentum Microscopically the tissue changes are similar to those of schistosomiasis mansoni

Manifestations Following penetration of cer cariae through the skin allergic manifestations such as urticaria itching localized dermatitis cough and angioneurotic edema accompanied by fever and diarrhea may appear Four to six weeks after exposure gastrointestinal symptoms are evident a result of ulcerations produced in the intestinal walls by the large number of eggs Bloody mucoid stools or periods of bloody diarrhea accompanied by ab dominal pain may be present If untreated symp toms may last for several months The liver en larges and becomes tender and splenomegaly de velops

As the disease progresses the spleen becomes larger and the size of the liver decreases Signs of portal obstruction such as engorgement of super ficial abdominal veins ascites etc appear The patient may succumb from hemorrhage due to rupture of esophageal varices Some individuals present marked splenomegaly a small contracted liver profound anemia leukopenia and thrombo cytopenia associated with severe malnutrition and hypoproteinemia The majority of individuals suf fering from schistosomiasis japonica die of cirrhosis and cachexia massive hemorrhage from rupture of esophageal varices or intercurrent infections

Diagnosis and Laboratory Findings The charac teristic ova must be found in the stools in order to establish the diagnosis In established cases ova are more difficult to demonstrate in the stools or in rectal biopsy and the intradermal skin test is of value Aqueous extracts of cercariae or of adult worms are employed

Treatment Tartar emetic and Fuadin have been employed in doses somewhat higher than those used in schistosomiasis mansoni In general *S japonicum* infections are more difficult to treat and relapses are more frequent Miracil D (Nilodin lucanthone hydrochloride) a synthetic nonmetallic compound containing a xanthone nucleus has been employed by the oral route It is absorbed rapidly and 60 mg per kilogram daily in divided doses given for a period of 3 to 6 days is the recommended dosage Mild toxic reactions such as abdominal pain weak ness nausea and vomiting have occurred and re sults have not been very successful

Prognosis If the condition is not treated early prognosis is poor in the majority of cases encoun tered in endemic communities

SCHISTOSOMIASIS HAEMATOBIA (Genitourinary Schistosomiasis Endemic Hematuria)

Etiology and Life Cycle The male worm has an average length of 1 3 cm and a breadth of 0 09

accompany urticaria Anorexia headache generalized aches and pains and diarrhea accompanied by abdominal discomfort soon follow and last 1 to 2 weeks These symptoms occur after invasion of the parasite and during the periods of migration of the larvae or cercariae From 30 to 70 days following exposure when the cercariae have become adult males and females and oviposition has occurred more severe symptoms appear In some cases there is high fever (39 to 40 C) with chills and abdominal discomfort Diarrhea and melena are common A persistent dry cough is present and scattered fine or coarse rales can be heard over the chest The peripheral blood shows an eosinophilic leukocytosis and ova are usually found in the stools The findings in the peripheral blood excepted the clinical picture resembles typhoid fever or paratyphoid fever This acute illness usually lasts from 1 to 3 months and subsides by lysis When the initial infection is not severe or when anthelmintic treatment is given the patient may recover rapidly but should the infection remain untreated intermittent bloody diarrhea frequently lasts several months The severity and duration of these symptoms depend upon the extent of the initial infection In untreated cases however several years may pass without signs of visceral disease Should reinfection occur fever and severe gastrointestinal symptoms again ensue Anemia at times severe enough to cause invalidism may be present as the result of chronic blood loss In many cases the liver and the spleen become enlarged

The late stage of the disease frequently gives rise to a new clinical picture The manifestations at this time resemble Banti s syndrome with emaciation hepatosplenomegaly ascites and other evidences of hepatic cirrhosis and portal hypertension Some patients develop leukopenia thrombocytopenia and macrocytic anemia However the bone marrow shows no megaloblastic arrest Liver function tests are frequently abnormal Massive hematemesis from ruptured gastroesophageal varices is a frequent cause of death and hepatic insufficiency is not uncommon In Egypt rectal and colonic polyposis prolapse of the rectum and intestinal obstruction are common late manifestations of the disease

In some patients particularly adolescents in whom irreversible vascular changes have occurred in the lungs pulmonary hypertension associated with chronic cor pulmonale dominate the clinical picture and a form of Ayerza s disease ensues This may overshadow the already present hepatic cirrhosis and portal hypertension

Diagnosis and Laboratory Findings Diagnosis of the condition must be made by finding the ova in the stools in the rectal mucosa or rarely in the urine Various techniques of stool concentration are available and the reader is referred to texts on clinical parasitology for technical details By the use of such methods greater numbers of eggs are picked up from a given specimen and a larger number of cases may be detected The intradermal skin test employing cercaria or worm extract possesses diagnostic value in suspected cases where no ova can be found in the stools or in the rectal biopsy Serodiagnosis particularly the circumoval precipitin reaction shows promising results By means of a Jackson s laryngoscopic forceps 35 cm long a piece of mucosa 2 to 3 mm in diameter can be readily obtained through a proctoscope When this unstained tissue is compressed between two glass slides the ova can be recognized easily under the low power lens of a microscope It is believed by many investigators that rectal biopsy is the most reliable method of diagnosis a very small piece of tissue may contain up to several hundred ova In many cases in which repeated stool examinations have been negative rectal biopsy has shown living or dead ova Occasionally however stools contain ova when biopsy is negative

Bilirubinemia and jaundice are seen rarely even in the presence of advanced cirrhosis

Treatment Certain trivalent antimony compounds have been found effective against *S mansoni* These are tartar emetic (antimony potassium tartrate) stibophen (Fuadin) and Anthiomaline Tartar emetic is one of the more toxic antimony compounds It is administered intravenously in a freshly prepared solution in initial dose of 0 06 Gm increasing to a maximum of 0 12 Gm by the third dose and continued every other day until a total of 2 2 Gm has been given A second course may be given after 1 month Antimony sodium tartrate —less toxic than the potassium salt—is being employed with great success Fuadin is antimony pyrocatechin sodium sulfonate and contains 13 per cent trivalent antimony *It has the advantage of* intramuscular administration It is well tolerated and produces a minimum of toxic reactions when given in courses of not over 50 to 60 ml each Daily injections of 1 5 3 5 and 5 ml are given for the first 3 days to be continued every other day with 5 ml doses until a complete course has been administered The effectiveness of Fuadin as an anthelmintic is believed to be not greater than 50 to 60 per cent Antimony lithium thiomalate (Anthiomaline) is administered intramuscularly in 2 to 3 ml doses every other day until a total of 30 to 40 ml is given comprising one course Lucanthone hydrochloride (Miracil D) has been employed with promising results This drug has the advantage of being active by the oral route

The disappearance of eggs from the stools and improvement in *symptomatology constitute the criteria* for evaluation of anthelmintic therapy Ex

perience has shown that for a period of about 1 month following administration of either Fuadin or Anthiomaline stool examination and rectal biopsy may give negative results which are misleading It is preferable to give several Fuadin courses (50 to 60 ml) a year if the tolerance of the patient permits Toxic manifestations occur in 20 to 30 per cent of the patients Pain at the site of the injection and generalized arthralgia are common however hepatitis acute nephritis and thrombocytopenic purpura have been observed Triostam (sodium antimonyl gluconate) has been used with success It is well tolerated and toxic reactions are rare One disadvantage is that the drug must be administered intravenously In the late stages of the disease these therapeutic measures are palliative since the patient is suffering from cirrhosis of the liver portal hypertension or hypersplenism The indications for surgical procedures are the same as for the other forms of portal hypertension (p 1507)

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As the disease progresses the spleen becomes larger and the size of the liver decreases Signs of portal obstruction such as engorgement of superficial abdominal veins ascites etc appear The patient may succumb from hemorrhage due to rupture of esophageal varices Some individuals present marked splenomegaly a small contracted liver profound anemia leukopenia and thrombocytopenia associated with severe malnutrition and hypoproteinemia The majority of individuals suffering from schistosomiasis japonica die of cirrhosis and cachexia massive hemorrhage from rupture of esophageal varices or intercurrent infections

Diagnosis and Laboratory Findings The characteristic ova must be found in the stools in order to establish the diagnosis In established cases ova are more difficult to demonstrate in the stools or in rectal biopsy and the intradermal skin test is of value Aqueous extracts of cercariae or of adult worms are employed

Treatment Tartar emetic and Fuadin have been employed in doses somewhat higher than those used in schistosomiasis mansoni In general *S japonicum* infections are more difficult to treat and relapses are more frequent *Miracil D* (*Nilodin lucanthone hydrochloride*) a synthetic nonmetallic compound containing a xanthone nucleus has been employed by the oral route It is absorbed rapidly and 60 mg per kilogram daily in divided doses given for a period of 3 to 6 days is the recommended dosage Mild toxic reactions such as abdominal pain weakness nausea and vomiting have occurred and results have not been very successful

Prognosis If the condition is not treated early prognosis is poor in the majority of cases encountered in endemic communities

SCHISTOSOMIASIS HAEMATOBIA (Genitourinary Schistosomiasis Endemic Hematuria)

Etiology and Life Cycle The male worm has an average length of 1 3 cm and a breadth of 0 09

cm The female is long and slender averaging 2 0 cm in length and 0 025 cm in breadth The eggs are compact elongated spindles dilated in the middle and measuring about 140 μ by about 50 μ At one pole they present a short stout terminal spine The ova are passed in the urine and occasionally in the feces The life cycle is similar to that of S *mansoni* The adult worms live in the hemorrhoidal plexus of veins some going to the rectum for oviposition but most of them passing on to the vesical plexus The intermediate hosts are snails of the genera *Bulinus Physopsis* and *Lymnaea*

Pathology In the urinary bladder large numbers of ova are deposited in the submucosa and give rise to dense infiltration with eosinophils lymphocytes and plasma cells These foci or pseudoabscesses" apparently represent an allergic reaction to the eggs but even though many of the eosinophils undergo necrosis and fragmentation the lesion is not a true abscess The mucosa becomes thickened and ulcerated The trigone is involved at first but soon the entire bladder is affected In chronic infections the other coats become scarred and the muscularis hypertrophies Pedunculated papillomas often develop at the trigone and about the urethral orifices The bladder capacity becomes greatly reduced as the organ loses its contractility Lesions occur in the distal third of the ureters in many cases causing obstruction and hydronephrosis In about 10 per cent of cases calculi develop in the bladder renal pelvis or ureters Fistulas between the urogenital tract and intestines may develop The prostate and seminal vesicles may be affected and lymph blockage may produce an elephantoid condition of the genitalia The cervix and vagina can be infected by extension from the bladder Carcinoma of the bladder is a frequent late complication

Manifestations Painful micturition frequency and hematuria are the leading symptoms Secondary bacterial infection of the urinary tract is frequent and repeated hemorrhages from the bladder produce severe anemia

Diagnosis and Laboratory Findings As in the other types of schistosomiasis diagnosis is made by finding the characteristic ova in the urinary sediment in tissues obtained from vesical mucosa or less frequently in the stools

Treatment Chemotherapy is effective early in the disease but is contraindicated when urinary obstruction and infection have supervened Lucanthone hydrochloride (Miracil D) appears to be more efficient (80 to 85 per cent) than Fuadin and nearly as effective as intensive treatment with intravenous antimony sodium tartrate Triostam (sodium antimonyl gluconate) has been found to be effective against infection with S *haematobium* Surgery may be required for abscesses fistulas strictures papillomas and various other complications involving the bladder The criteria of cure are the absence of ova in the urine and bladder wall and the disappearance of ulcerative and granulomatous lesions as revealed by cystoscopic examination

Prognosis Provided treatment is given early prognosis is good in recent infection fair when damage to the bladder and urinary infection have already occurred and very poor in chronic late infections After age forty five the mortality rate increases fourfold The frequent coexistence of infection with S *mansoni* aggravates prognosis and the clinical picture

SCHISTOSOME DERMATITIS

Definition and Geographic Distributions Cort demonstrated that certain nonhuman schistosome cercariae may penetrate the skin of man and cause a dermatitis This condition is known as *schistosome dermatitis* or swimmer s itch" and is common in many parts of the world The condition apparently does not develop after a single contact with cercariae but it ensues following multiple exposures Definitive hosts of some of the schistosomes producing dermatitis are the muskrat and migratory birds Again snails are intermediate hosts

Schistosome dermatitis has been reported from the fresh water areas of north central United States Canada Oregon Central America Western Europe (particularly Switzerland) and the Far East

A sea water dermatitis believed to be produced by nonhuman schistosome cercariae has been reported in New York Rhode Island California, Hawaii and Florida

Pathogenesis and Clinical Manifestations Because the dermatitis develops only after multiple exposures the condition is believed to represent an allergic reaction the nonhuman cercariae being the sensitizing agents Exposed individuals show positive intradermal reaction when tested with cercarial antigen

Treatment Local application of antipruritic lotions such as calamine with menthol or phenol is used to allay itching and thereby to reduce the likelihood of secondary infection Local treatment with antihistaminic drugs will relieve the pruritus

Prevention Immediate drying of the skin after swimming has been recommended as a prophylactic measure This will not completely prevent lesions since some penetration occurs during immersion Dimethyl phthalate cream has been reported as an effective cercarial repellent

In some areas control has been effected by destruction of snails Copper sulfate and copper car

bonate have been used for this purpose Treatment of shallow waters where snails are abundant has been moderately effective

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202 OTHER TREMATODES OR FLUKES

Gustave J Dammin

Paragonimiasis

Paragonimiasis also known as *endemic hemoptysis* is an infection, primarily of the lung caused by *Paragonimus westermani* In addition to man also the dog cat, pig rat and some wild carnivores serve as definitive hosts The characteristic cystlike pulmonary lesions measure up to about 1 cm in diameter and when of long standing have a stout wall composed of fibrous connective tissue Other smaller lesions may be in the form of nodules representing reaction around deposited eggs Eggs appear in the feces when sputum from pulmonary lesions is swallowed In heavy infections lesions may also be found in the liver mesentery skeletal muscle and brain According to the sites of predominant involvement, cases may be classified as pulmonary abdominal or cerebral *In the pulmonary type* abundant brownish sputum is produced and bouts of hemoptysis occur Abdominal pain and dysentery characterize the abdominal type Various types of paralysis and epilepsy are observed with cerebral involvement Eosinophilia is rather constant in all varieties of paragonimiasis Eggs should be searched for in the sputum and feces in attempting to establish the diagnosis By using an antigen prepared from the adult trematodes complement fixing antibodies can be demonstrated This may be helpful in identifying occult abdominal and cerebral infections

Treatment with emetine hydrochloride as prescribed for fascioliasis affords symptomatic relief However there is no specific effective therapeutic agent Prevention of superimposed infections is important, since the infection is in a sense self limiting

Paragonimiasis has probably the widest geographic distribution of any of the diseases produced by *the hermaphroditic trematodes It is endemic* in many parts of the Far East and has been reported from parts of Africa and northern South America

The most practicable control measure is the adequate cooking of all shellfish to be used as food, since infection is acquired by ingestion of cysts in the second intermediate host, such as a crab crayfish or mollusk.

Clonorchiasis

Definition. Clonorchiasis is an infection caused by *Clonorchis sinensis* and is characterized by *hepatic lesions produced by the adult worms in the biliary passages*

Etiology *Clonorchis sinensis* the most important liver fluke in man is a hermaphroditic worm measuring about 15 mm by 5 mm Infection of man follows on ingestion of raw fish containing the larval *Clonorchis* Many fish-eating mammals can serve as definitive hosts (dog, cat, pig, badger guinea pig, and others) The encysted larva is released and migrates from the duodenum into the

biliary tract where it develops into the adult form Judging from studies on individuals who have left the Far East the major endemic area the adult *Clonorchis* is capable of living as long as twenty five years

Clinical Manifestations The percentage of asymptomatic infections is probably high The bile ducts become thickened and dilated and there is chronic pericholangitis and atrophy of parenchyma but cirrhosis with the usual clinical manifestations is uncommon

Laboratory Diagnosis The diagnosis usually depends on the demonstration of the eggs in the feces or the duodenal contents

Treatment No method of treatment has been consistently successful but some success has been noted with gentian violet and chloroquine diphosphate Gentian violet may be given as for strongyloidiasis Chloroquine is prescribed in a dose of 0 25 Gm twice daily for 28 days Most infections will respond to this dosage those which do not should be treated for an additional 2 to 3 week period

Prevention Adequate cooking of fresh water fish will prevent infection

Opisthorchiasis

Opisthorchiasis is caused by *Opisthorchis felineus* and is characterized by hepatic lesions occasioned by the presence of the adult worms in the larger bile ducts The life cycle resembles that of *Clonorchis sinensis* with lesions and clinical manifestations like those produced by *C sinensis* The geographic distribution differs in that it is endemic in Eastern and Central Europe and in Siberia and occurs in some parts of Asia The diagnosis usually is based on the finding of the eggs in the feces or duodenal contents Treatment as recommended for clonorchiasis may be used Infection can be prevented by eating only well cooked fish

Fascioliasis

Fascioliasis is caused by the hermaphroditic leaf shaped fluke *Fasciola hepatica* which inhabits the bile ducts of the definitive host When fully matured the adult measures about 3 cm by 1 cm and discharges large operculate eggs 140 mm by 70 mm

Fascioliasis produces so called "liver rot in the sheep the principal definitive host The disease is most common in sheep and cattle raising countries but has been reported from many parts of the world On the North American continent it occurs in the southern and western United States Central America and in the Caribbean islands

Infection is contracted by ingestion of the encysted form attached to edible aquatic plants such as water cress

Early clinical manifestations are related to the migration of the larval form to and within the liver Epigastric pain fever diarrhea jaundice urticaria pruritis arthralgia and eosinophilia may be observed during this stage Cirrhosis of the liver of the variety found in clonorchiasis may be a late manifestation appearing only after prolonged residence of many adult worms in the bile ducts A pharyngeal form of the disease may follow on the ingestion of infected raw liver the young adults attaching themselves to the pharyngeal mucosa occasionally interfering with respiration

The diagnosis usually is based on the finding of the eggs in the feces or in the duodenal contents It is difficult to distinguish the eggs from those of *Fasciolopsis buski*

The therapeutic agent by choice is emetine hydrochloride given intramuscularly The dose should not exceed 1 mg per kilogram body weight or a total daily dose of 60 mg in these amounts it should not be given for more than 6 to 7 days Thirty milligrams per day has been given for as long as 18 days with good results It should be given only when there is ample opportunity for rest in bed It should not be given to patients with chronic cardiac or renal disease or to children

To prevent infection in man aquatic plants such as water cress should not be eaten vegetables grown in fields irrigated with polluted water should be boiled and safe drinking water should be provided

Fasciolopsiasis

Fasciolopsiasis is caused by the large intestinal fluke *Fasciolopsis buski* which inhabits the upper intestine of its definitive host The principal definitive host is the pig In parts of China India and other parts of the Far East infection of man is common Infection is contracted following ingestion or peeling with the teeth of water chestnuts and other edible aquatic plants The large adults attach themselves to the intestinal mucosa and these sites may later ulcerate Diarrhea and abdominal pain appear early Later if heavy infection continues asthenia with ascites and anasarca occurs Diagnosis is based upon the history and the finding of eggs in the feces The eggs resemble those of *Fasciola hepatica* The prognosis in untreated heavy infections especially in children is poor Hexylresorcinol administered as for trichuriasis is the preferred therapeutic agent and can be expected to cure or markedly reduce the worm burden in the majority of cases The most practicable control measure is the brief immersion of all edible aquatic plants in boiling water

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203 CESTODES OR TAPEWORMS

Gustave J Dammin

Diphyllobothrium Latum

Definition *Diphyllobothrium latum* the fish tapeworm or broad tapeworm produces in man and its other definitive hosts infection characterized by the presence of the hermaphroditic adult worm in the intestinal lumen

Etiology The adult worm may measure from 5 to 10 m and possess between 3 000 and 4 000 proglottids (Fig 151) The mature proglottids measure about 3 to 5 mm in length and 10 to 15 mm in width The stage in the infected fresh water fish the host from which man acquires infection is known as the *plerocercoid larva* or *Sparganum* It is found in large numbers in the muscles and other tissues of the fish

Pathogenesis Ingestion of infected fish in the uncooked state by man the dog the cat or the bear results in infection The larva develops into the adult form in the intestine in about 3 weeks and is then capable of discharging eggs The adults

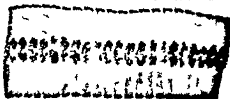


Fig 151 Gravid proglottids of *Diphyllobothrium latum* (×2)

of *D latum* have been known to survive for periods of 5 to 10 years

Distribution Fish tapeworm infection is common in the Baltic and Scandinavian countries Switzerland Italy Russia, Japan Chile and Central Africa. It has also been established in the north central United States, south central Canada and Florida

Clinical Manifestations Most infections either are asymptomatic or produce slight transient abdominal discomfort Infrequently severe cramping abdominal pain vomiting weakness and loss of weight are noted

Pernicious tapeworm anemia with erythrocyte counts ranging from half a million to two million has many features in common with Addisonian pernicious anemia, including central nervous system involvement It differs from the latter in that patients produce intrinsic factor but do not respond when given beef extract (extrinsic factor) and normal gastric juice (intrinsic factor) while the tapeworm is still present. Removal of the tapeworm and the administration of extrinsic factor leads to clinical and hematologic improvement The position of the tapeworm in the intestine is important anemia occurring only when the tapeworm is in the proximal small intestine Large amounts of vitamin B_{12} have been demonstrated in the tapeworm presumably absorbed from the host's intestine *Taenia saginata* which does not produce pernicious tapeworm anemia contains about 2 per cent as much vitamin B_{12} as *D latum* The appearance of pernicious tapeworm anemia is related to vitamin B_{12} absorption and possibly also to a decreased production of intrinsic factor and decreased supply of extrinsic factor It is apparent, however that the tapeworm and the host compete for vitamin B_{12} There may be ethnic and geographic factors involved since most cases are reported from the Baltic countries none to date has been reported in this country

Treatment. Atabrine has supplanted oleoresin of aspidium and carbon tetrachloride If prescribed as for taeniasis saginata, Atabrine can be expected to cure most infections In the presence of severe macrocytic anemia, an adequate response to parenteral vitamin B_{12} should be obtained before an anthelmintic is used

Prevention The most practical control measure is the thorough cooking of all fresh water fish Children should not be permitted access to fish markets or to kitchens when fresh water fish is being prepared because of the possibility that some larvae may be ingested To reduce contamination of waterways dogs and cats should not be fed raw fresh water fish

Sparganosis

The *Sparganum* or plerocercoid larva of *Diphyllobothrium mansoni* will develop in man following ingestion usually in drinking water of a *Cyclops* bearing the procercoid larva Sparganosis also follows application of infected fresh frog flesh used as a poultice The frog tissues contain the *Sparganum which is capable of invading human tissues* The dog and cat are definitive hosts for *D mansoni* The location of the larvae determines the prognosis of the infection in man Surgery and local alcohol injection are the only methods of treatment

Sparganum proliferum the adult stage of which is unknown produces a more severe infection because of its unusual multiplication in the human host Nodules containing the larvae form in the skin lungs intestine brain and other sites The prognosis is poor in severe infections

Sparganum mansonoides probably accounts for most of the cases of sparganosis observed in the United States

Taeniasis Saginata

Definition *Taenia saginata* the beef tapeworm is a hermaphroditic cestode which inhabits the intestinal tract of man its only definitive host

Etiology and Pathogenesis In its adult stage the *T saginata* measures from 5 to 10 m in length and possesses about a thousand proglottids The gravid proglottid (Fig 152) measures about 5 mm in width and 20 mm in length It possesses 15 to 30 lateral uterine branches thus distinguishing it from *T solium* which has 8 to 12 The proglottids may show independent motion for long periods after discharge with the feces The head or scolex measures 1 to 2 mm in diameter and possesses prominent suckers but no hooks The eggs are ovoid 30 μ by 40 μ and are indistinguishable from those of *T solium* When the eggs are ingested by cattle the embryo is released in the intestine invades the intestinal wall and is carried by vascular channels to striated muscle in the hind limbs diaphragm and tongue the common sites for formation of the cysticercus stage (*Cysticercus bovis*) *C bovis* measure about 5 mm by 10 mm and consists of a scolex held in a cystlike structure When *C bovis* is ingested in raw or undercooked beef by man the adult tapeworm develops in the intestine in about 2 months

Distribution Taeniasis saginata occurs in countries in which it is the custom to eat raw or undercooked beef It has been estimated that in the USSR alone there are about eighteen million infections and in the world s population almost forty million Although not common in the United States beef tapeworm infection is the most prevalent tapeworm infection observed in the northern half of this country

Clinical Manifestations Symptoms usually consist of mild epigastric pain diarrhea hunger sensations weight loss irritability nausea and rarely an increase in appetite Movements of the worm may be apparent to the host Rarely segments may become impacted in the vermiform appendix with almost simultaneous development of appendicitis *Approximately one fourth of the infections are* asymptomatic

Laboratory Findings The diagnosis is usually made by the finding of proglottids in the feces When the history suggests that proglottids may have been passed but none are immediately available for examination the perianal region should be examined as for pinworm infection using the Scotch tape swab By this method 85 to 95 per cent of infections may be detected whereas by stool examination only 50 to 75 per cent can be recognized When the scolex is obtained it may be examined for suckers and the absence of rostellum and hooks to identify it as *T saginata* The above study is necessary since the ova observed in the feces cannot be distinguished from those of *T solium* A slight eosinophilia may accompany this infection

Treatment Carbon tetrachloride and aspidium oleoresin have long been accepted as efficacious but their occasional toxicity has stimulated search for other agents

Experience with Atabrine has shown it to be a highly efficacious agent which has the advantage of ease of administration The evening before the Atabrine is to be administered the patient takes 30 Gm of sodium sulfate in a glass of water The following morning while still fasting he takes 1 Gm Atabrine followed with a glass of water in which 1 teaspoonful of sodium bicarbonate has been dissolved Two hours later a second dose of sodium sulfate similar to the first is taken When successful such treatment will remove the entire worm which will be found to be stained yellow If the scolex has not been removed regeneration of the tapeworm will occur and retreatment may be necessary in 2 to 3 months

Incomplete removal by Atabrine has been followed by complete removal of the tapeworm subsequent to the administration of Benadryl in Emplet form

Prevention The only practical means of preventing infection is the thorough cooking of beef Tem

peratures as low as 71 C for as little as 5 minutes will destroy *C bovis* Refrigeration and salting for prolonged periods also destroy the *Cysticercus* Adequate meat inspection and disposal of human excreta will also aid in control but are costly and seldom practical

Taeniasis Solium

Definition *Taenia solium* the pork tapeworm usually manifests itself as a parasite of man by inhabiting the intestinal lumen Man is the only definitive host but under some circumstances may act also as the intermediate host harboring the larval stage *Cysticercus cellulosae* The usual intermediate host is the hog

Distribution Taeniasis solium has a world wide distribution but is commonest in the USSR Asia and Africa

Etiology and Pathogenesis The hermaphroditic adult tapeworm measures about 3 m in length and possesses a globular scolex containing a rostellum with about two dozen hooklets There are seldom more than a thousand proglottids The gravid proglottid measures about 6 mm in width and 12 mm in length and contains a uterus with 8 to 12 lateral branchings The eggs resemble those of *T saginata* When ingested by the hog the embryo is released from the egg penetrates the intestinal wall and is carried by vascular channels to all parts of the body Localization with development to the encysted larval stage *C cellulosae* (bladder worm) occurs predominantly in striated muscle particularly that of the tongue neck and girdle muscles The cysticerci are ovoid gray white opalescent structures measuring about 1 cm in diameter An opaque white spot denotes the site of the scolex Man becomes infected following ingestion of undercooked pork containing cysticerci The scolex is freed and attaches itself to the intestinal mucosa and development to the adult stage begins at this time

Clinical Manifestations Clinical manifestations related to the presence of the adult tapeworm resemble those associated with *T saginata* The manifestations differ when man serves as the intermediate host This may occur following ingestion of the eggs or the return of gravid segments to the stomach by reverse peristalsis The released embryo bores into the intestinal wall and is distributed by vascular channels to various parts of the body Cysticerci develop in the subcutaneous tissues in muscles in viscera and—of most significance—in the eye and brain Only moderate tissue reaction occurs while the scolex is viable The dead larva however behaves like a foreign body and provokes a marked tissue response Symptoms are related to active larval encystment only in heavy infections Muscular pains weakness and slight fever may be observed The involvement in the brain may be in

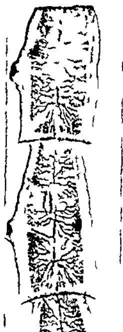


Fig 152 Gravid proglottids of *Taenia saginata* (×2)

the form of a meningoencephalitis when the cysticerci are widely distributed However epilepsy brain tumor encephalitis and other types of neurologic disorder may be simulated Eosinophilic leukocytosis of the blood and spinal fluid accompanying such clinical manifestations suggests cerebral cysticercosis Degenerate cysticerci ultimately calcify

As in other tapeworm infections a slight to moderate eosinophilia is a fairly constant finding The finding of eggs in perianal scrapings or in the feces will identify the infection as taeniasis For a specific diagnosis proglottids or the scolex must be examined As in beef tapeworm infection the diagnosis is usually made by finding proglottids in the feces Roentgenographic demonstration of calcified foci may aid in diagnosis of cysticercosis The prognosis is in large part determined by the stage and location of the parasite Surgery may be indicated in cerebral and ocular cysticercosis

Treatment For removal of the worm in the adult stage see p 1138

Prevention The simplest and most effective preventive measure is the thorough cooking of pork Treatment of recognized cases will reduce the hazard of larval stage development as well as the spread of the infection

Echinococciasis

Definition Echinococciasis may be caused by the larval stage of *Echinococcus granulosus* or *E multilocularis* These species of echinococcus are distinct morphologically and biologically In man

Prevention The most practical control measure is the thorough cooking of all fresh water fish Children should not be permitted access to fish markets or to kitchens when fresh water fish is being prepared because of the possibility that some larvae may be ingested To reduce contamination of waterways dogs and cats should not be fed raw fresh water fish

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Prevention The only practical means of preventing infection is the thorough cooking of beef Tem

Fig 153 Daughter cysts occur frequently in large old unilocular hydatid cysts They are thin walled balloons formed by herniations of the wall of the mother cyst and lie free in the cyst fluid Free hooklets are also found floating in this fluid (*Ash and Spitz Pathology of Tropical Diseases Philadelphia W B Saunders Company*)

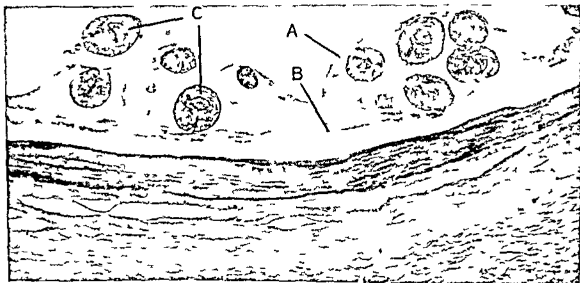


Fig 154 Brood capsules are vesicles of single cell layer (*A*) which arise from the germinal membrane (*B*) Invaginated scolices (*C*) arise as buds from the inner surface of the brood capsule (*Ash and Spitz "Pathology of Tropical Diseases Philadelphia W B Saunders Company*)

E granulosus produces cystic expanding lesions involving the liver and lungs primarily whereas the lesions of *E multilocularis* are destructive because of their invasive character

Etiology *Echinococcus granulosus* infection in man cattle sheep horses and hogs the principal intermediate hosts is contracted by ingestion of the eggs present in the feces of the dog the principal definitive host Following ingestion the embryos escape from the eggs penetrate the intestinal mucosa and enter venous and lymphatic channels Some soon arrive in the liver and may form hydatid cysts there and those entering the lymphatics are carried ultimately to the lungs There is no exogenous budding from the wall of the cyst only endogenous Transmission to the definitive host occurs following ingestion of the hydatid cysts which contain scolices An adult worm may develop from each scolex in the intestine of the dog wolf coyote and other of the Canidae The adult is small measuring about 5 mm in length and consists of no more than 5 or 6 segments *Echinococcus multilocularis* infection is manifested by the same type of invasive larval produced lesion as is observed in the natural intermediate host for this stage the microtine rodents The adult or tapeworm stage is found in the dog and fox

Distribution Echinococciasis caused by *E granulosus* has its highest incidence in sheep and cattle raising countries particularly in North and South Africa Australia Central Europe and South America In Iceland a high incidence of infection in man and the dog has been markedly reduced by control measures In the southern western and southwestern areas of the United States the infection is established and a small number of cases reported each year *Echinococcus multilocularis* has been identified in Eurasia Alaska and the Kuriles and adjacent islands

Pathogenesis and Clinical Manifestations Two principal types of lesions develop in the intermediate host the unilocular type of *E granulosus* and the alveolar type of *E multilocularis* The former is more common grows slowly and consists of an external laminated cuticula and an inner germinal layer Fluid fills and distends the cyst Daughter cysts (Fig 153) and brood capsules (Fig 154) develop from the germinal layer representing endogenous development Hydatid sand found in the cyst consists of scolices liberated from ruptured brood capsules Exogenous development results from evagination of the cyst wall and ultimately produces the multilocular or alveolar type of lesion Metastatic lesions occur when growth extends into vessels

Symptoms produced depend upon the size attained by the cystic lesion and the amount of tissue destroyed Unilocular lesions may become barren following resolution of secondary bacterial infection Rupture into the peritoneal or pleural cavities may produce an anaphylactoid reaction which occasionally is fatal The unilocular type of hepatic lesion progresses slowly and is most amenable to surgical treatment The alveolar type progresses more rapidly with metastatic lesions developing in the bones brain and other sites Pathologic fractures occur and cerebral involvement may be manifested by epilepsy

Diagnosis and Treatment Clinical manifestations seldom are characteristic enough to suggest the diagnosis but roentgenographic appearance of the lesion especially when calcification is present is often helpful (Schlanger and Schlanger) Eosinophilia is suggestive although seldom present Inquiry should be made concerning residence in an endemic area and skin (Casoni or substitute antigen) and/or serologic tests performed before exploration is considered Exploration may be required as both a diagnostic and a therapeutic measure Because of serious reactions to the leakage of cyst fluid into the tissues and body cavities aspiration should be attempted only during exploration Aspirated cyst fluid should be examined carefully for scolices hooklets and laminated cyst wall The size of the lesion will determine whether excision or marsupialization is the procedure of choice Only surgical treatment offers hope of cure

Prevention In prevention (1) contact with infected dogs should be avoided particularly fecal contamination of the hands and food (2) infected carcasses and offal should be burned or buried in order to prevent access of dogs to material containing scolices and (3) dogs should be treated if found to be infected The reduction of the incidence of echinococciasis in Iceland is an example of the efficacy of control measures

Hymenolepiasis Nana

Definition Hymenolepiasis nana is an intestinal infection of man caused by *Hymenolepis nana* the dwarf tapeworm

Etiology The life cycle is unique in that both the larval and adult phases of development occur in the same host Man mice and rats readily contract infection upon ingestion of the eggs The adult measures about 2 cm in length and may possess over a hundred proglottids

Distribution The presence of dwarf tapeworm infection has been reported in temperate and tropical regions around the globe It is the commonest tapeworm found in the United States most of the infections occurring in the Southern states

Clinical Manifestations This tapeworm infection is characterized by the presence of many adult worms in the host's intestine When infection is massive diarrhea and abdominal pain occur

forward thrust of the head and the instant that the erect fangs make contact venom is expressed by sudden muscular contraction

The rattlesnakes recognized by the horny rattle on the tail which buzzes when the snake is disturbed are widely distributed The diamondbacks (*Crotalus adamanteus* in the Southeast and *C atrox* in the Southwest) are the largest and most dangerous snakes in this country Others include the prairie rattler (*C confluentus*) the timber rattler (*C horridus*) and the pigmy rattlers

The water moccasin or cottonmouth (*Agkistrodon piscivorus*) is found in swampy areas or along the banks of streams It is a strong swimmer and can bite under water This snake is notorious for inflicting severe facial bites when disturbed in the branches of small trees The copperhead or highland moccasin (*A mokasen*) is a closely related species Its bite is painful but rarely fatal

Pathogenesis *Snake Venoms* The venoms of many species have been analyzed invariably each proves to be a mixture of several toxic proteins and enzymes As an example the venom of the Indian cobra (*Naja naja*) contains these distinct and separate substances a neurotoxin a hemolysin a cardiotoxin a cholinesterase at least three phosphatases a nucleotidase and a potent inhibitor of cytochrome oxidase Several venoms including those of the pit vipers contain hyaluronidase and numerous proteolytic enzymes Although experts differ about the exact role of these components in toxicity the action of the venom of a given species is usually predominantly neurotoxic or necrotizing frequently associated changes are hemolysis and changes in blood coagulation The venom of elapids including the coral snake is neurotoxic and death results from respiratory paralysis probably caused by damage to brain centers and a curariform interference with transmission at the neuromuscular junction The venom of crotalid snakes produces local tissue injury hemorrhage and hemolysis death is preceded by circulatory collapse the mechanism of which is poorly understood Systemic absorption of venom occurs through lymphatics and therapeutic measures designed to reduce lymphatic function are helpful in controlling symptoms On rare occasions when venom is discharged directly into a blood vessel death occurs in less than 10 min

Factors Affecting Severity Several factors affect the outcome of snake bite

1 The age size and health of the patient Envenomation in children is usually serious and a fatal outcome more likely

2 Bites on extremities or into adipose tissues are less dangerous than those on the trunk or face or penetrating a vessel A direct stroke of the fangs is more dangerous than a scratch a glancing blow or one hitting a bone The discharge orifice of the fang is well above its tip and the point of the fang can penetrate the skin without envenomation Even a thin layer of clothing may afford great protection

3 The size of the snake the extent of its anger or fear (if hurt it may inject a large dose of venom) the condition of the venom glands (recently discharged or full) and the condition of the fangs (broken recently renewed) are all important

4 The presence of various bacteria in the mouth of the snake or on the skin of the victim (especially clostridia) may lead to serious infection in the necrotic tissues at the local site

5 Exercise or exertion such as running immediately after the bite speeds systemic absorption of toxin

Manifestations The bite of a pit viper produces severe pain at the local site within a few minutes There is rapid swelling ecchymoses and bullae appear over the involved areas and as the edema spreads serosanguinous fluid oozes from the puncture wounds Systemic effects include circulatory collapse with hypotension clammy skin tachycardia intense thirst nausea hematemesis bloody diarrhea icterus (rarely intense) hemorrhages from the nose and into the skin and convulsions Death may occur after 6 to 48 hr Survival may be attended by massive local tissue loss from gangrene and secondary infection amputation of an extremity is sometimes necessary Fever of 101 to 104 F polymorphonuclear leukocytosis of 20 000 to 30 000 and albuminuria appear within a few hours in severe cases

The bite of an elapine snake causes little pain and local swelling is slight There are usually multiple fang marks Numbness and weakness begin in the region of the bite within 10 to 15 min and are followed by ataxia ptosis pupillary dilatation and loss of reaction to light and accommodation, palatal and pharyngeal palsies slurring of speech salivation and occasionally nausea and vomiting The patient becomes comatose respirations falter there are convulsions and death occurs within 8 to 72 hr

Treatment An attempt should be made to determine with certainty that the patient has been bitten by a poisonous snake Absence of distinct fang punctures and failure of local pain edema numbness or weakness to appear within 20 min are strong evidence against a bite s having been inflicted by a venomous species

Treatment consists of immobilization application of a tourniquet incision and suction, antivenin refrigeration measures to combat infection and general support All patients should be transported to a hospital as quickly as possible

Local Measures A tourniquet should be placed a few centimeters above the bite (if anatomically feasible) and made tight enough to allow one finger

Treatment Atabrine as prescribed for taeniasis saginata (p 1138) is moderately effective

Prevention This is difficult since the problem is similar to that encountered in enterobiasis Only a single host is involved and the eggs are immediately infective Personal hygiene should be stressed The contamination of food by rats and mice should be prevented

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Section 19 Disorders Due to Venoms

204 SNAKE BITE

Ivan L Bennett Jr

Fewer than one tenth of the nearly 2 500 known species of snakes are venomous These poisonous varieties belong to five families or subfamilies Elapidae (cobras kraits coral snakes) found in all parts of the world but Europe Viperidae (true vipers) found in all parts of the world but the Americas Hydrophidae (sea snakes) Crotalidae (pit vipers) found in Asia and the Americas and Colubridae represented by a few rear fanged species of Africa The poisonous varieties of the United States with the single exception of the coral snake of the Elapidae are pit vipers and include the rattlesnakes the water moccasin and the copperhead This discussion will center around these species but the therapeutic measures outlined are applicable to snake bites in all parts of the world

The number of individuals bitten by poisonous snakes in the United States is estimated at 2 000 to 3 000 per year deaths are not reported separately but are undoubtedly rare numbering fewer than 20 per year In many European countries deaths from snake bite have averaged only one every 3 to 5 years for the last half century In contrast the estimate of annual deaths from snake bite in Brazil is 2 000 (4 per 100 000 population) and 2 000 in Burma (15 4 per 100 000)

Etiology The coral snake is found in the Southern states from Florida to Arizona It is marked by alternating red and black bands separated by yellow rings Coral snakes are nocturnal and placid and rarely bite man The fangs are short and permanently erect the highly toxic venom is injected into multiple puncture wounds produced by a series of chewing movements

The pit vipers are so named because of a small pit between the eye and the nostril Large venom glands in the temporal region give the head a triangular appearance They are generally aggressive and likely to strike if disturbed The fangs are long and hinged folding posteriorly when the mouth is closed Pit vipers strike suddenly with a

can species These reptiles are not aggressive and virtually every instance of their attacking man has involved teasing or handling the animals in captivity The venom is elaborated in eight glands in the floor of the mouth and secreted directly into the oral cavity where it bathes the teeth which are grooved posteriorly The lizard clings tenaciously and is often dislodged only after considerable effort envenomation occurs by contamination of the wound The venom contains a potent neurotoxin which is undoubtedly responsible for its lethal effect in experimental animals Death in man has been reported as occurring within a few hours (in one case 30 min) after a bite The venom also produces local tissue injury excruciating pain massive edema and patchy erythema In recovered cases acute symptoms have lasted for 3 to 4 days and include nausea vomiting hematemesis blurred vision dyspnea dysphonia and profound weakness Intense hyperesthesia of the bitten extremity can persist for several weeks There is no antivenin available Treatment should consist of tourniquet incision suction measures to prevent or combat infection including tetanus and supportive measures Because Demerol has been shown to potentiate the venom s action in animals some other analgesic should be used to relieve pain

Spider Bite

The bite of many spiders can be locally irritating and several species are capable of causing severe sometimes fatal systemic poisoning By far the most numerous and important venomous spiders are the members of the genus *Latrodectus* which is widely distributed throughout the world In the United States and Canada *L mactans* the black widow or shoe button spider is the cause of nearly all clinically significant arachnidism In Florida another species *L bishopi* the red legged widow spider has been reported to produ e human poisoning resembling mild black widow bite The symptomatology and mortality from bites of large hairy spiders the tarantulas such as *Lycosa raptoria* and *Phoneutria fera* in Brazil and *Glyptocranium gasteracanthoides* in Peru differ in no important respects from those produced by *Lactrodectus* except that there is also severe necrosis and ulceration at the site of a tarantula bite

It is the female *L mactans* the black widow that bites man She is glossy black with a body 1 cm in diameter and a leg span of 5 cm There is a characteristic red hourglass" mark on the ventral abdomen (Fig 155) She spins her web in wood piles sheds basements or outdoor toilets is very aggressive and bites on slight provocation The venom is said to be about fifteen times as potent as that of the rattlesnake on a weight for weight basis It produces diffuse central and peripheral nervous excitement, autonomic activity muscle spasm hypertension and vasoconstriction

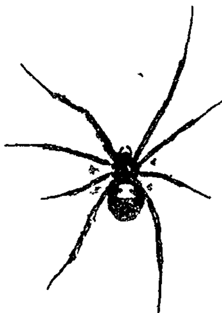


Fig 155 *Latrodectus mactans* female (black widow) Ventral surface showing the orange red "hourglass" spot (Approximately actual size) (*Stitt Strong "Diagnosis Prevention and Treatment of Tropical Diseases"* The Blakiston Division *McGraw Hill Book Company Inc New York*)

In the United States most spider bites occur between April and October and many patients are males bitten on the genitalia or buttocks while using a privy After a momentary sharp pain at the site there is cramping pain that begins locally within 15 to 60 min and gradually spreads It can involve all extremities and the trunk The abdomen is boardlike and the waves of pain become excruciating causing the patient to turn toss and cry out Respirations are often labored and grunting There are also nausea vomiting headache sweating salivation hyperactive reflexes twitching tremor paresthesias of hands and feet and occasionally systolic hypertension A mild polymorphonuclear leukocytosis is usual and many patients have fever up to 100 F After several hours the pains subside although mild recurrences for 2 or 3 days are common It may be a week before well being is restored Deaths have occurred mostly in children and the aged In an analysis of nearly 1 300 cases from the United States and Canada

to pass beneath it with difficulty The purpose is to impede lymph flow and it is not necessary to obstruct venous return the tourniquet should be *loosened* and *moved proximally* when local swelling causes it to tighten Using whatever antisepsis is available 1 cm cruciate incisions about 0 5 cm deep should be made through each fang mark and suction applied for at least 30 min A rubber bulb for this purpose is contained in first aid kits but a breast pump funnel attached to a vacuum line or heated jar can be used Mouth suction is permissible if no oral lesions are present Suction should be carried out for 15 min every hr then every 2 hr as long as fluid is obtainable As the swelling progresses successive rings of radiating linear shallow incisions at the advancing edge of the edema are useful such cuts will be expanded by the *progressive swelling* Once a patient has been hospitalized a pavex boot is a convenient means of applying suction to an extremity Extensive or deep slashes over the area are unnecessary Incision and suction are extremely important and should be carried out diligently in every poisonous snake bite Antivenin is not a substitute for them and should not be relied on alone

Immobilization of the affected part during transportation is important in controlling lymph flow splinting is useful in achieving this The application of ice packs to the affected area reduces inflammation and swelling slows drainage by lymphatics relieves pain and curtails local necrosis Care should be taken to avoid freezing the tissues

Antivenin Many of the components of venom are antigenic and effective antiserum can be prepared by inoculation of horses with graded doses In this country the only commercially available antivenin is *Antivenin Crotalidae Polyvalent (North and South American Antisnakebite Serum)* prepared by Wyeth Laboratories it is effective against all pit vipers Kits containing lyophilized antivenin (reconstituted with distilled water to 10 ml per ampul) syringe normal horse serum for prior sensitivity testing of the patient and detailed instructions are available The initial dose for a serious bite should be 5 ampuls intramuscularly and if antivenin is given within 2 hr after the bite 10 ml of this can be infiltrated locally Further antivenin can be given as indicated by progression of swelling or systemic symptoms

No antivenin for coral snakes is manufactured in the United States although antiserum is sometimes kept on hand in large zoos Soro Anti Elapidico is the commercial name of an effective serum against coral snake venom that is available from the Instituto Butantan Caixa Postal 65 Sao Paulo Brazil

The American Association for the Advancement of Science Symposium on Venoms listed among the references at the end of this chapter contains a complete listing of antivenin preparations and their sources throughout the world

Other Measures The maintenance of respiration by manual or mechanical aids is important in patients bitten by the elapine snakes It has been suggested that the cholinesterase of cobra and coral venom is responsible for much of the neurotoxicity and that neostigmine and atropine given as for myasthenia gravis might help This has not been tested clinically

Tetanus toxoid or antiserum should be given If pyogenic infection develops antibiotics should be used

Alcohol has no place in the treatment of snake bite Opiates are contraindicated Relief of pain with salicylates or Demerol sedation maintenance of fluid intake measures to combat shock and appropriate management of coma or convulsions are all important

Limited trials of ACTH and adrenal steroids have not shown any great usefulness of these hormones in lessening local necrosis or systemic intoxication

Prevention In snake infested regions long trousers high shoes boots or leggings and gloves should be worn Most important of all is to look where one steps or reaches A sharp knife or lancet tourniquet suction bulb and antiseptic suffice for an emergency kit and in inaccessible areas antivenin also should be carried

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205 OTHER DISORDERS DUE TO VENOMS

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Gila Monster Bite

The Gila monsters include the large orange and black lizard (*Heloderma suspectum*) of the arid Southwest and *H horridum* a closely related Mexi

Cheyne Stokes breathing Pulmonary edema develops terminally The patient passes from an agitated state with hyperactive reflexes into coma convulsions follow Death usually occurs within 12 hr but sometimes as late as 2 days after the sting

Treatment This consists of immediately placing a tight ligature on the extremity just proximal to the sting followed by application of ice and as soon as possible immersion of the involved member above the ligature in ice water The ligature must be removed in 5 to 10 min but the limb is kept refrigerated for at least 2 hr After this time if treatment has been applied promptly it is said that no serious effects are experienced following the sting of *C sculpturatus* or *C gertschi* If the sting is on the head trunk or genitalia of course the ligature cannot be used but the area may be chilled with an ice pack

Other authors recommend tourniquet incision and suction as in the treatment of snake bite However the amount of venom is minute it produces no local necrotizing effect and is absorbed so rapidly that unless these procedures are carried out very promptly they are of doubtful value

Supportive therapy is directed at combating shock and dehydration Barbiturates in large doses are useful in reducing restlessness

Prevention This depends upon alertness in avoiding contact with scorpions in infested areas Clothing and shoes should be well shaken before being put on in the morning Towels and bedclothes should be inspected A house infested with scorpions can in time be rid of them by closing all obvious ways of ingress picking up debris in the environment such as piles of brush logs stones introducing a mixture of fuel oil or kerosene containing a small amount of creosote between the earth and the house foundation and spraying with a mixture of 2 per cent chlordane 10 per cent DDT and 0 2 per cent pyrethrins in an oil spray base The spray is applied in a band 3 ft wide to the outer walls to the undersurface of the house also to screens and crevices around windows and plumbing and under the eaves Inside the house the attic woodwork plumbing cupboard and closet interiors are similarly coated with the residual spray which under protected conditions has proved effective for as long as 6 months

Tick Paralysis

Tick paralysis is a reversible disorder of the nervous system which sometimes develops in the host while a tick is engorging It may occur in man or animals The disease has been reported from many countries It has long been recognized in the northwestern United States and western Canada where the wood tick *Dermacentor andersoni* Stiles is responsible More recently the dog tick *D variabilis* Say has been identified in a number of cases occurring in the Eastern states *Amblyomma americanum* the lone star tick and *A maculatum* the Gulf Coast tick have also been incriminated

While engorging the tick apparently injects a neurotoxin which acts upon the spinal cord and bulbar nuclei causing incoordination weakness and paralysis The toxin is rapidly destroyed or excreted for when the tick is removed the nerve cells soon regain normal function

Tick paralysis has been produced in experimental animals only with gravid female ticks suggesting that the toxin might be elaborated by the ova However injection of extracts prepared from tick eggs has failed to reproduce the clinical picture in convincing fashion

The tick must feed for several days before symptoms develop Female ticks commonly remain attached for 7 to 9 days or longer Paralysis is seen in experimental animals after 5 to 7 days of engorgement Male ticks feed for a shorter period a fact which may explain why they are less likely to cause paralysis

Experimental confirmation of the theory that the toxin is produced in tick salivary glands is also lacking It has been found that not all gravid female ticks of incriminated species cause paralysis The nature site of production and mode of action of the toxin have not been established

Most human cases occur in children generally in young girls The tick is usually attached to the scalp and hidden by the hair but may be found on any part of the body especially the ear axilla groin vulva or popliteal region Both white and Negro races are susceptible

The patient may be irritable for 24 hr before motor involvement appears Mild diarrhea may occur There is weakness and poor control of the legs The tendon reflexes in the legs are diminished or absent and the Romberg sign is positive Temporary improvement may occur and if the tick is removed at this stage true paralysis may never develop Otherwise the symptoms recur within 24 hr with flaccid paralysis which extends in one or more days to involve the trunk arms neck tongue and pharynx Sensory changes are usually absent but there may be paresthesia and hyperesthesia in the affected extremities Nystagmus strabismus and facial paralysis are sometimes noted The respirations become shallow rapid and finally irregular The patient sinks into stupor cyanosis appears and death results from respiratory paralysis or from obstruction of the airway by aspirated material

There is little or no fever unless a secondary

the mortality varied from 2 4 to 6 0 per cent This is higher than is usually stated

Because the bite itself is not prominent patients are often thought to have some abdominal catastrophe such as perforated ulcer pancreatitis or volvulus Renal colic coronary occlusion tetanus strychnine poisoning tabetic crisis lead colic and porphyria are other conditions to be ruled out The abdomen is not tender to palpation in arachnidism and pains in the extremities are not typical of most of these other disorders

Treatment This consists of antiserum and measures to relieve pain The antiserum is produced in horses by Merck Sharp and Dohme and a single intramuscular injection of one ampul (2 5 ml) of reconstituted material is all that is needed in most cases relief is gradual Hot baths alleviate pain temporarily and intravenous calcium gluconate or magnesium sulfate will produce dramatic but usually transient cessation of cramps Opiates are usually incompletely effective Neostigmine epinephrine and ACTH have all been reported to give relief in isolated cases and are worth trying

Bee Sting

Bee venom is hemolytic and neurotoxic and has a histaminelike action Multiple stings in man cause pain and discomfort but only in enormous numbers (500 to 1 000) can they cause death Apiarists become immune to the venom and can sustain many stings without effect

The usual reaction to a single bee or wasp sting is sharp pain local wheal and erythema intense itching and in loose tissues such as the eyelid or genitalia considerable local edema This subsides in a few hours Only in the rare case when a bee is inhaled or swallowed and edema of the laryngopharynx or glottis develops is there danger A sting directly into a peripheral nerve may destroy its function for a time much as does an injection of alcohol There have for example been cases of Bell s palsy following sting into the trunk of the facial nerve

In hypersensitive individuals a single sting may produce serious anaphylaxis with urticaria nausea abdominal cramps asthma massive edema of the face and glottis dyspnea cyanosis hypotension coma and death Sensitization is usually a result of previous stings beekeepers sometimes develop allergic rhinitis followed by asthma when near bees or objects that have been in contact with bees These individuals are likely to have serious reactions to a sting

Treatment The usual sting is treated by local cool applications and antipruritic lotions or oral antihistaminics Epinephrine 0 3 to 0 5 ml of 1 1000 aqueous solution subcutaneously repeated every 20 to 30 min may be lifesaving in allergic patients This drug can be given as 1 100 solution in oil intramuscularly Oxygen antihistaminic drugs and other supportive measures should be used Desensitization by injections of extracts of whole bees has been reported but if this is not practical *contact with bees should be avoided*

Scorpion Sting

Scorpions are eight legged arthropods Adults are 2 to 20 cm in length Glands in the terminal segment produce venom which is injected into the victim by a stinger located on the tip of the tail Scorpions often enter dwellings During the day they retreat into crevices emerging at night they often get into shoes and clothing and even into bedding They do not deliberately attack man but accidental contact results in a sting

Of about 650 species roughly 40 occur in the United States distributed over three fourths of the nation They are most numerous in the South from Florida to California but the only two lethal species *Centruroides sculpturatus* and *C gertschi* are limited to Arizona and portions of neighboring states In general scorpions are not encountered in New England and the Great Lakes area

The venom is neurotoxic It acts locally upon sensory nerves and centrally upon the medulla and involuntary nervous system causing circulatory respiratory and widespread autonomic disturbances

Dangerous species found in the United States *C sculpturatus* and *C gertschi* reach a maximal length of about 7 cm Their sting may be fatal to young children or old people but seldom to a healthy adult In the years 1929 to 1948 inclusive 68 deaths from scorpion sting were reported from the state of Arizona

Most of the nonlethal species of scorpions in the United States cause only minor reactions like a bee sting Some in the Southwest however produce local edema and ecchymosis with burning pain In contrast many species whose venom has potentially dangerous systemic effects including the Arizona *Centruroides* evoke little or no visible reaction at the site of the sting There is an immediate burning sensation followed by local paresthesia (pins and needles) hyperesthesia or numbness These spread to involve the whole extremity and within an hour or two malaise restlessness lacrimation rhinorrhea salivation perspiration nausea and vomiting appear The emeses may contain blood Transient hypertension glycosuria and premature ventricular contractions have been recorded In fatal cases dyspnea may occur without cyanosis Tachycardia with muffled heart sounds and feeble pulse may be noted or there may be bradycardia and respiratory depression with irregular or

Etiology Sarcoidosis attacks persons of all ages but is most likely to be encountered between the ages of twenty and forty It is probably quite a common affection and though Scandinavia is the cradle of the disease cases have been reported from most countries in Europe from Africa South America Japan and in increasing numbers from the United States In North America the Negro appears to be particularly susceptible and in this race the disease is recognized at a much earlier age than in the white Both sexes are affected equally

The incidence of the disease does not suggest a hereditary basis but there are accounts of families with two or more members suffering from it The disease often affects farm laborers or those who live in country districts In a study of military personnel a significantly greater frequency was noted among those whose birthplace had been in the southeastern United States

The cause is unknown On histologic grounds *there is considerable resemblance between sarcoidosis* and the effects of known bacterial infections such as tuberculosis leprosy and brucellosis fungous invasions and the effects of particulate matter such as beryllium but no relationship to any of these has been demonstrated Many regard the disorder as infectious in origin It is noteworthy that patients with sarcoid are more often refractory to tuberculin than are normal persons of comparable age sex, and race

Morbid Anatomy The characteristic lesion is a granuloma consisting of large pale epithelioid cells collected in isolated nests or well defined nodules the so-called "hard tubercles Pale multinucleated giant cells containing peculiar basophilic inclusions may be present Necrosis or caseation does not occur and there is no inflammatory zone about the clusters of epithelioid cells The evolution of the lesion is very slow but fibrosis ultimately develops Calcification does not take place The characteristic granulomas may be found in many parts of the body including the skin lymph nodes lungs bone marrow spleen liver mucous membranes salivary and lacrimal glands eye tonsil myocardium nervous system kidney prostate breast and testis The manifestations of the disease depend on the location of the lesions and may be those resulting from involvement of the lungs (polycythemia cor pulmonale) heart (arrhythmia failure) liver (hyperglobulinemia) thyroid (myxedema) pituitary (diabetes insipidus) nervous system (especially pareses and paralyses) kidneys (renal insufficiency) or testes (eunuchoidism)

Symptoms The onset is insidious as a rule the progress sluggish and the dissemination of the lesions is wide There is slow healing but relapse is frequent The condition harms essentially not by intoxication but by mechanical injury Longcope aptly stated that in its irregular progression with regressions and exacerbations and in its long periods of hidden latency sarcoidosis can only be compared to syphilis and tuberculosis while in its distribution throughout the body it can be likened to Hodgkin s disease

In uveoparotid fever after a period of malaise lassitude and indefinite gastrointestinal symptoms intermittent pyrexia of moderate degree may occur The parotid glands enlarge and are firm but painless Often one gland is affected later than the other The mouth may become very dry Uveitis usually follows the parotid involvement Conjunctivitis keratitis neuroretinitis or other types of ocular involvement may occur Seventh nerve paralysis unilateral or bilateral may follow or there may be other evidences of cranial nerve involvement or signs of a peripheral neuritis in one of the extremities may appear

Skin eruptions have been observed in 15 to 60 per cent of cases They may consist of (1) small discrete slightly elevated nodules varying in size from a few millimeters to a centimeter in diameter yellowish or purplish in color waxy in appearance and sometimes pitted in the center or umbilicated These are found usually over the face about the eyelids and nares or over the ears and around the shoulders and the upper extremities (2) large more or less lobulated granulomata which are firm and dry and frequently have a purplish tint These occur most conspicuously on the nose or about the joints of the hands and feet and (3) large flat very finely granular or scaly plaques that usually cover large areas of the skin principally over the extremities or trunk Pustulation and ulceration do not occur in any of the lesions but atrophic scars may remain when the lesions ultimately subside

Firm nodules may appear at the interphalangeal joints of the hands producing sometimes a knotty appearance There may be tightness or stiffness of the fingers In about 17 per cent of cases roentgenograms reveal rarefaction and trabeculation of the medullary portions of the shafts of the phalanges and metacarpal bones or punched out areas may be present in the small bones of the hands and feet (*osteitis tuberculosa multiplex cystoides*)

In other cases general lymphadenopathy attracts attention first The cervical submaxillary epitrochlear axillary and inguinal nodes may be involved but preauricular postauricular submaxillary and submental involvement are particularly suggestive of sarcoidosis The individual nodes are usually moderate in size firm in consistency discrete and not tender At the same time it is common to find that there is enlargement of lymph nodes in the

thorax especially in the hilar region where they may be massive (potato nodes) and in the peri bronchial and peritracheal area

Of all the internal organs the lungs are the most susceptible to involvement by sarcoidosis The lesions may be (1) miliary with tiny densities appearing throughout the whole lung field (2) linear extending fanwise from the hilum (3) nodular (4) diffuse and confluent or (5) combinations of these *The pulmonary disease may be asymptomatic* or pulmonary functional abnormalities may occur as reduced lung volume with mild hyperventilation and inconstant decrease in maximum breathing capacity or disturbances in alveolar capillary gas exchange (syndrome of alveolar capillary block) or the pattern may be that of chronic pulmonary emphysema

The cardiovascular system may sustain damage indirectly from the pulmonary disease or there may be direct invasion of the heart muscle Dyspnea and cyanosis are characteristic features of such cases

In the abdomen the lymph nodes the liver and the spleen are the most susceptible sites of the disease Although the intestinal tract is rarely affected the stomach may be involved and massive hemorrhage may occur Hepatic enlargement is the usual manifestation of disease in the liver but liver biopsy reveals focal granulomas in many cases There may be impaired Bromsulphalein excretion and other evidences of hepatic dysfunction Hyperbilirubinemia and frank jaundice are rare

Slight to moderate splenic enlargement has been observed in at least 25 per cent of the cases This may be accompanied by anemia leukopenia thrombocytopenia purpura signs of portal hypertension or no symptoms or signs whatever

In addition to fever at the onset of the disease when this is acute and when in particular it takes the form of uveoparotid fever fever of considerable *degree may be present with exacerbations of the* disease and in the late stages when extensive pulmonary lesions are present

Renal insufficiency renal calculi and nephrocalcinosis in addition to hypercalcemia are manifestations of sarcoidosis which may cause considerable confusion in diagnosis and may ultimately lead to death Granulomatous lesions are sometimes associated with the renal failure *but the latter may* occur even in their absence and is then accompanied by hypercalcemia and nephrocalcinosis and even hypercalcuria and renal calculi The cause of the hypercalcemia is obscure It is not necessarily related to widespread bone destruction *Increased* gastrointestinal absorption of calcium has been demonstrated in several cases and excessive endogenous production of vitamin D like substances has been postulated as the cause In some cases hypersensitivity to vitamin D seems to have been an aggravating factor

Laboratory Findings Anemia is unusual The leukocytes may be normal in number or there may be slight leukopenia Eosinophilia (6 to 35 per cent) and monocytosis have been noted in a number of cases The total plasma proteins are usually increased as a result of an increase in the gamma *globulin The serum calcium is often above normal* the phosphatase sometimes Pleocytosis and increased protein in the spinal fluid may be associated with the uveoparotid syndrome

Diagnosis The characteristic features of the skin lesions which suggest this disease are their occur*rence in groups bilaterally their persistence and* slow extension and their lack of tendency to ulcerate The finding or history of parotid swelling and uveal tract involvement perhaps with facial nerve palsy the invasion of the lacrimal and salivary glands the lymph node involvement and the lesions in the small bones of the hands and feet offer evidence strongly suggestive of sarcoidosis Slit lamp examination may disclose minute bodies typical of sarcoid in the iris or cornea

It is not rare however for these typical features to be lacking yet the finding sometimes accidental of enlarged hilar nodes or shadows in the lungs the existence of slight fever or a little weight loss vague abdominal pain or splenic or hepatic enlargement the discovery of lymphadenopathy or the presence of unexplained hemolytic anemia leukopenia or thrombocytopenic purpura demands intensive study and a search for the cause

Hodgkin s disease and tuberculosis in particular must be ruled out In sarcoidosis the constitutional reaction considering the degree of involvement is singularly inconspicuous as compared with that expected in Hodgkin s disease or tuberculosis and the Mantoux reaction and sputum are negative Silicosis *may be suggested by the pulmonary lesions* syphilis by the bone lesions and leprosy by the skin changes Periosteal changes are found in syphilis not in sarcoidosis The benign course and lack of constitutional symptoms rule out leprosy

Establishment of the diagnosis depends on biopsy of affected structures whenever possible Even small lymph nodes may show characteristic *changes When there is a pulmonary lesion* scalenus fat pad biopsy may reveal epithelioid cell granulomas Liver aspiration biopsy is also very useful and splenic and bone marrow biopsies are sometimes employed

The Nickerson Kveim cutaneous reaction has been found to be helpful in diagnosis and the incidence of false positive reactions is claimed to be low The test consists of the intradermal injec

tion of a heat sterilized suspension of human sarcoid tissue and histologic examination of the site of injection after 4 to 6 weeks As the disease process regresses the test result may become negative but positive responses have been observed in a few patients whose illness had begun even a decade earlier

Prognosis Spontaneous recovery may be anticipated in the majority of cases but the condition is apt to run a long course during which relapses with involvement of different organs and tissues alternate with quiescent or latent periods Death may result from the accumulation of sarcoids in the mediastinum lungs heart or central nervous system The uveoparotid syndrome usually disappears but some thickening of the parotid may persist and scars synechias and even blindness may follow eye involvement Renal failure may result from nephrocalcinosis Tuberculosis has been demonstrated in approximately 30 per cent of cases coming to autopsy

Treatment A variety of remedies have been tried including tuberculin arsenic gold ultraviolet rays roentgen rays radium and nitrogen mustard but their efficacy is difficult to assess Of greatest promise is the use of ACTH or cortisone With these agents a striking regression of signs and symptoms of active disease has been observed in many cases However the pattern of events after cessation of treatment has varied from prolonged remission to prompt relapse Where the disease has produced extensive fibrotic change little if any improvement has been observed

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207 INFECTIOUS MONONUCLEOSIS

M M Wintrobe

Definition This is a disorder of unknown etiology usually benign and probably of infectious origin which is characterized by irregular fever sore throat lymphadenopathy and enlargement of the spleen as well as by an absolute lymphocytosis made up of cells of a peculiar type High concentrations of antibodies against sheep erythrocytes are usually demonstrable in the blood serum

History Since the designation "infectious mononucleosis" was first proposed by Sprunt and Evans in 1920 an ever increasing number of cases has been observed and reported especially since 1935 This is due at least in part to better recognition of the disease Prior to 1920 a few sporadic cases had been observed The relationship of epidemics in children described under the title of "glandular fever to infectious mononucleosis is uncertain

Etiology and Pathogenesis This is a disease of young people including children which has now been observed practically throughout the world In the United States infectious mononucleosis has been less frequent in Negroes than in white persons It is a relatively common condition in interns medical students and nurses but many cases among other persons undoubtedly pass unnoticed The mild or nonspecific character of many of the symptoms may be responsible or the fact that appropriate blood examinations have not been made With increasing frequency sporadic cases have been observed wherever young people live together as in boarding schools colleges and military groups

The etiology is unknown although it is generally believed that the disease is infectious in nature It is likely that individual susceptibility is low and that the causative agent is extremely labile No clear instances of successful experimental transmission to human subjects have been reported and in the main experiments both in man and in animals have yielded little knowledge as to the nature of the causative agent

Clinical Picture The clinical picture differs to some extent in accordance with the stage of the disease In the *prodromal period* which may be 3 to 6 days in duration the symptoms may be vague and nonspecific such as chilly sensations and slight fever malaise sore throat swollen

Table 98 SYMPTOMS AND SIGNS OF INFECTIOUS MONONUCLEOSIS EXCLUDING FEVER AND HEADACHE

Prodromata or early symptoms	*Per cent*	*1st and 2d week symptoms (excluding malaise)*	*Per cent*	*Late and/or convalescent signs and symptoms*
Malaise	51	Swollen cervical glands	77	Glands may remain enlarged for weeks—a small percent age
Sore throat	49	General glandular enlargement	70	Severe cases may leave the pa tients feeling below par for months
Swollen cervical glands	21	Throat		
Chills	20	Red	57	
Cough	12	Sore	50	
Eyes sore or pain back of eyes	10	Spleen enlarged	43	
Neck sore and stiff	9	Stomatitis and/or Vincent s angina	36	
Abdominal pain	7	Rash	15	
Pain in shoulder	4	Eye signs *	15	
		Liver enlarged	13	
		Jaundice	5	
		Cough	3	

* *These include swollen eyelids 5% conjunctivitis 5% pain in or back of eye 9%* photophobia *4%*
SOURCE Gardner and Paul Yale J Biol and Med 19 846 1947

cervical glands stiff neck and occasionally cough The temperature curve is irregular rising each evening to a higher level In the *midstage* the clin ical picture is more characteristic although the manifestations of this disorder are protean In this second week of the illness cervical glandular en largement is a very common sign (77 per cent of cases) and often the adenopathy is generalized The glands are single or in clumps but they are usually discrete and only slightly tender except where they drain a secondarily infected area The throat is often sore and in more than half the cases a brilliant red color can be observed in the pharynx over the arches soft palate and uvula At the same time there may be a translucent edema involving the soft palate and the uvula Such edema may be present even when there is no pain in the throat In other cases the throat presents the typical picture of follicular tonsillitis or that of Vincent s angina or of diphtheria Stomatitis may be present

A diffuse or patchy often morbilliform" rash usually limited to the trunk eye signs (conjunc tivitis pain in or back of the eyes photophobia) and jaundice may be encountered in various cases The liver may be found enlarged even in the ab- sence of jaundice and liver function tests indicate that hepatic involvement without symptoms is com mon The spleen is palpable in more than half the cases

This midstage lasts from 4 to 20 days and is followed by a *period of convalescence* which some times is slow and may be associated with marked prostration Recrudescences are very common Re lapse has occurred in about 6 per cent of cases Recovery is the rule but death has been observed in a few instances from such complications as rupture of the spleen respiratory paralysis in asso- ciation with nervous system involvement pneu monia edema of the glottis and hemorrhage from a deep tonsillar ulceration

Classification of infectious mononucleosis under the headings (1) glandular form (2) anginose type and (3) febrile type emphasizes the three most common forms of the disease but fails to make clear that this is a disorder of very diverse mani festations ranging from cases with no fever or con stitutional symptoms to those with severe prostrat ing complaints of great variety Headache may be so severe as to suggest meningitis Epistaxis pur pura hematuria rectal bleeding marked tachy cardia with cyanosis electrocardiographic evidence of cardiac involvement convulsions stupor coma stiff neck and various pareses and paralyses in volving cranial nerves or lower motor neurons are among other symptoms and signs which may de velop Involvement of mesenteric nodes may be as sociated with signs which mimic acute appendi citis

Blood Picture The leukocyte count is usually increased but in the first week especially there may be leukopenia due to granulocytopenia The leuko- cytosis is usually moderate (10 000 to 15 000 per cubic millimeter) but it may sometimes be very marked It is due to an increase in lymphocytes and these in the main are of a peculiar type their nucleus may be oval kidney shaped or slightly lobulated and the cytoplasm is often somewhat basophilic and may be vacuolated or foamy in ap pearance The nuclear chromatin is usually coarse and irregular and nucleoli are rarely seen These

cells make up 60 per cent or more of all the leukocytes

The characteristic changes in the leukocytes may appear as early as the second day of illness or as late as the twelfth day They attain a peak by the seventh to tenth day and persist usually for 1 to 2 months

Anemia is extremely rare but several instances of hemolytic anemia complicating infectious mononucleosis have been reported Thrombocytopenia is rare but in several cases the clinical picture resembled that of idiopathic thrombocytopenic purpura The bone marrow reveals a slight myeloid hyperplasia and immaturity there may be an increase in lymphocytes

The serum characteristically contains agglutinins against sheep red cells in high titer (heterophil antibodies Paul Bunnell test see Chap 109) This has been observed in different series in 60 to 100 per cent of cases The Paul Bunnell test is actually nonspecific Anti sheep agglutinins are present in titers up to 1 28 in most normal persons and occasionally even in a titer of 1 56 In various infections a titer of 1 112 and occasionally of 1 224 may be seen Persons receiving injections of horse serum and horse immune serum may develop titers as high as any seen in infectious mononucleosis For these reasons it is generally considered that in the presence of clinical and hematologic findings suggestive of infectious mononucleosis a titer of 1 224 or higher can be interpreted as confirming the diagnosis When there is doubt a differential test is required This is based on the observation that heterophil antibodies in normal serum in horse serum sensitization and in a variety of infections can be absorbed completely by guinea pig kidney On the other hand anti sheep agglutinins in infectious mononucleosis are never completely removed by treating the serum with guinea pig kidney although they are as a rule completely removed by beef red cells The differential test is carried out by absorbing a portion of the patient s serum with guinea pig kidney and an other portion with beef red cells After this the absorbed specimens are tested for sheep red cell agglutination

In infectious mononucleosis highest heterophil antibody titers are found usually during the second and third weeks of illness and as a rule positive reactions last 4 to 8 weeks The titer bears no relation to the severity of the disease or the degree of lymphocytosis The serologic test for syphilis may become transiently positive

Renal function is rarely impaired but albumin and red cells may be found in the *urine* The *cerebrospinal fluid* pressure may be moderately elevated and pleocytosis due to lymphocytes may be found

Diagnosis While glandular enlargement, sore throat fever the characteristic cells in the blood and an increased titer of heterophil antibodies are a combination of findings which makes recognition of this disease easy in many instances the protean manifestations of infectious mononucleosis may produce a clinical picture which taxes the acumen of the physician Acute appendicitis German measles follicular tonsillitis infectious hepatitis and influenza are a few of the diseases which may be simulated Acute leukemia is another But anemia the presence of very immature leukocytes and of nucleated red cells in the blood and thrombocytopenia as well as the characteristic bone marrow picture should make differentiation not difficult

As already indicated the clinical picture and the blood findings may be so characteristic that a diagnosis of infectious mononucleosis can be made at times with reasonable assurance in the absence of a positive heterophil antibody reaction A rising titer as the disease progresses is of significance even if the increase is only within the "normal" range In the absence of the characteristic blood picture the diagnosis of infectious mononucleosis is unjustified unless well-defined changes in heterophil antibodies are observed

The clinical picture may be like that of serum sickness a condition in which lymphocytes quite similar to those seen in infectious mononucleosis may be found and as indicated above a positive heterophil antibody test may be obtained The differential test is required to distinguish between the antibody reactions in infectious mononucleosis and the rise in titer produced by horse serum Lymphocytosis relative or absolute may be encountered regularly or occasionally in a number of the diseases with which infectious mononucleosis may be confused on clinical grounds Marked leukocytosis (40 000 or even higher) chiefly due to the presence of small lymphocytes of normal appearance characterizes a benign disorder *acute infectious lymphocytosis* which has been observed chiefly in children and is accompanied by only mild constitutional manifestations and no lymphadenopathy splenomegaly or positive heterophil agglutination reactions

Treatment It is treated symptomatically Controlled studies indicate that neither penicillin nor Aureomycin has any significant influence on the disease The irregular fever persists in most cases for 1 to 3 weeks and subjective symptoms disappear as a rule in 2 to 4 weeks *Relapses* are not uncommon and may be late but recurrences are very rare A positive heterophil antibody reaction may persist for as long as 5 or 6 months rarely longer Anamnestic reactions of heterophil antibodies in significant titers have not been described

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208 REITER S SYNDROME

Max Michael Jr

Definition The eponym *Reiter s syndrome* designates a symptom complex comprising the triad of urethritis arthritis and conjunctivitis At times a diarrhea occurs and a variety of other visceral lesions may be present

Etiology and Epidemiology The etiology is unknown but the weight of evidence has incriminated either directly or indirectly members of the pleuropneumonia like group of organisms and the dysentery bacilli The earlier findings of a spirochete in the blood of a patient with the syndrome has not been corroborated Pleuropneumonia like organisms have been isolated from the urethra of a few patients with Reiter s syndrome and in rare instances these bacteria have been recovered from synovial fluid Since these organisms are difficult to detect it is possible that they may play an important etiologic role that has been overlooked for technical reasons Clinical observations have also suggested that bacillary dysentery is responsible for the development of the syndrome During the years 1943-46 344 cases of Reiter s syndrome were observed on the Karelian Isthmus where bacillary dysentery was endemic Whereas the incidence of Reiter s syndrome was 0 2 per cent in patients with dysentery dysentery preceded the onset of the syndrome in 96 4 per cent of the cases In the United States however it has been unusual to observe this relationship Reiter s syndrome usually affects young adult males and has only rarely been recorded in females and Negroes Whether sexual exposure constitutes the mode of infection remains a disputed point

Pathology A limited number of microscopic examinations of synovial tissue have been carried out These have demonstrated villous formation hyperemia and infiltrates of lymphocytes plasma cells and a few polymorphonuclear leukocytes The cellular infiltrates do not assume the nodular pattern observed in rheumatoid arthritis and pannus formation has not been observed

Clinical Features Urethritis conjunctivitis and polyarthritis usually follow each other in that order from 2 to 40 days or longer being required for the complete syndrome to manifest itself The *urethritis* varies from a slight serous discharge to a profuse purulent one It is as a rule more scanty than is that of gonorrhea The urethritis is of short duration in most instances and ceases before the onset of arthritis In those cases in which it persists for several months symptoms wax and wane Occasionally there is gross hematuria

Conjunctivitis usually bilateral varies from mild injection of the bulbar conjunctivas to an intense purulent inflammation Its duration is variable but is shorter than that of the arthritis It usually heals leaving no residua Keratitis iridocyclitis and corneal ulceration are occasionally noted *Arthritis* is most often polyarticular and involves principally weight bearing joints—in particular ankles and knees The small joints are only occasionally involved Joint pain is frequently of sudden onset several joints being affected within 2 or 3 days Heat redness and swelling both articular and periarticular are noted The splinting resulting from intensive muscle spasm can lead to contractures and deformities unless appropriate preventive measures are undertaken Arthralgia without objective findings is rare Arthritis persists from one month to over a year It always remains after the other features of the syndrome have subsided Involvement of tendons tendon sheaths and bursae may be noted

Other Manifestations Reiter s syndrome shows cutaneous lesions resembling keratodermia blennorrhagica ulcerations of the penis ulcerative lesions of the oral cavity cystitis proteinuria pleuritis pericarditis and myocarditis Mucocutaneous lesions seen most frequently in the genitourinary tract consist of small vesicles surrounded by an

erythematous papule The vesicle soon ruptures leaving a purulent crust which may become keratotic Splitting of the layers of the finger and toe nails as well as thick horny layers of the nails may be seen Diarrhea which is usually mild has been reported to precede many cases of Reiter syndrome by several weeks The occurrence of diarrhea as mentioned above has been particularly striking in the various series reported from military hospitals and in Finnish studies

The course of Reiter's syndrome is exceedingly variable Some patients are afebrile during the entire disease others may develop fevers as high as 104 F during the early stage of the disease The usual case shows low grade fever ranging from 100 to 101 F for about 2 weeks Recurrences which may occur from weeks to years after the initial episode are characteristic of the syndrome The recurrence may assume the pattern of the original attack or may consist of any combination of the triad It is probable that permanent joint destructive changes do not take place however contractures and muscle atrophy are not uncommon

Diagnosis By definition the diagnosis of Reiter's syndrome should be limited to those cases presenting the classic triad There has been a tendency to accept some cases in which certain features of the syndrome are lacking The chief diagnostic problem lies in its differentiation from gonococcal arthritis in which urethritis conjunctivitis and arthritis may occur Careful culture studies and the use of the gonococcal complement fixation test will usually clear up the dilemma (p 877) Rheumatoid arthritis may be confused with Reiter's syndrome particularly before the complete triad has developed Skin lesions and urethritis are rare in rheumatoid arthritis Moreover the arthritis of Reiter's syndrome is usually asymmetrical does not involve the interphalangeal joints as a rule and is only rarely accompanied by destruction of cartilage The differential sheep cell agglutination may be helpful (p 1720) Stevens-Johnson (p 1770) and Behcet's (p 1710) syndromes should cause no difficulty in differentiation as arthritis is rare in these entities and when present is mild

Treatment Salicylates are of value for the relief of pain The physical measures of rest heat massage muscle setting exercises and splints such as described for patients with rheumatoid arthritis should be undertaken (p 1721) Various authors have reported good results with either streptomycin or the broad spectrum antibiotics Possibly such results represent only the natural course of the disease with spontaneous remission but a trial of these agents for 10 days is warranted Adrenal corticoids and ACTH have been effective in ameliorating the acute inflammatory disease of eyes and joints and in permitting earlier and more active physiotherapy but the disease often flares up when hormones are discontinued

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209 MIDLINE GRANULOMA

Lawrence E Shulman

Definition This peculiar condition, also known as *lethal midline granuloma* or *granuloma gangraenescens* is characterized by progressive destruction of the soft tissues and bony structures of the face terminating almost invariably in death after several months or a few years of illness It occurs in young adults and the middle aged and seems to be more common in males The first case was described by McBride in 1897 More than 100 cases have been reported mostly in the otolaryngologic literature

Etiology and Pathology Not only is the etiology of midline granuloma unknown but it is uncertain in which category of disease it belongs There is disagreement as to whether it is primarily (1) infectious (2) vascular or allergic or (3) neoplastic Only a few complete and detailed autopsy studies have been reported In half of them lesions have been found in parts of the body other than the face notably in skin lungs and mesenteric lymph nodes

Histologically the lesions of midline granuloma vary from case to case and also from one area to another in the individual case The most common finding in the facial lesions is nonspecific chronic inflammation In the face and elsewhere there are focal areas of necrosis and necrotic small blood vessels often containing granular thrombi suggesting that the process is primarily vascular The vascular lesions however differ from those of polyarteritis nodosa in that the characteristic inflammatory reaction is absent The lesions in some areas contain large numbers of cells of varying sizes with large pale multilobulated nuclei simulating Hodgkin's disease and mycosis fungoides In other areas hyperchromatic nuclei and numerous mitotic figures resemble those seen in undifferentiated tumors

Clinical Features Midline granuloma begins with a prodromal period of months to years of nasal obstruction and discharge at first mucoid and later purulent During this time the patient is usually thought to have allergic rhinitis or sinusitis Pro

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209 MIDLINE GRANULOMA

Lawrence E Shulman

Definition This peculiar condition also known as *lethal midline granuloma* or *granuloma gangraenescens* is characterized by progressive destruction of the soft tissues and bony structures of the face terminating almost invariably in death after several months or a few years of illness It occurs in young adults and the middle aged and seems to be more common in males The first case was described by McBride in 1897 More than 100 cases have been reported mostly in the otolaryngologic literature

Etiology and Pathology Not only is the etiology of midline granuloma unknown but it is uncertain in which category of disease it belongs There is disagreement as to whether it is primarily (1) infectious (2) vascular or allergic or (3) neoplastic Only a few complete and detailed autopsy studies have been reported In half of them lesions have been found in parts of the body other than the face notably in skin lungs and mesenteric lymph nodes

Histologically the lesions of midline granuloma vary from case to case and also from one area to another in the individual case The most common finding in the facial lesions is nonspecific chronic inflammation In the face and elsewhere there are focal areas of necrosis and necrotic small blood vessels often containing granular thrombi suggesting that the process is primarily vascular The vascular lesions however differ from those of polyarteritis nodosa in that the characteristic inflammatory reaction is absent The lesions in some areas contain large numbers of cells of varying sizes with large pale multilobulated nuclei simulating Hodgkin s disease and mycosis fungoides In other areas hyperchromatic nuclei and numerous mitotic figures resemble those seen in undifferentiated tumors

Clinical Features Midline granuloma begins with a prodromal period of months to years of nasal obstruction and discharge at first mucoid and later purulent During this time the patient is usually thought to have allergic rhinitis or sinusitis Pro-

gressive inflammation and ulceration follow The first ulcerations are found in the nasal septum the mucosa or skin of the alae nasi or the center of the palate The lesions invade underlying cartilage and bone giving rise to septal or palatal perforations The condition spreads by local extension to involve the rest of the nose paranasal sinuses eyes mouth pharynx and larynx The bones of the midface are destroyed by erosion Gradually various important functions such as sight speech or ventilation are impaired or lost The end result is disappearance of most or all of the midface with the formation of a large cavity bounded above by the frontal bone and superior aspect of the orbits and below by the mandible which is never affected

During periods of activity and especially preterminally the patient becomes febrile Usually the fever does not respond to appropriate chemotherapy for secondary bacterial infection Moreover even in the presence of obvious pyogenic infection the patient often fails to develop leukocytosis and during the later stages may become chronically leukopenic Another curious feature is the absence of cervical lymphadenopathy during periods of active inflammation or infection A few patients showed raised indurated areas on the skin of the legs and abdomen resembling those of erythema nodosum *clinically and histologically There is no anemia and* the bone marrow is normal There are no serum protein abnormalities Microbiologic investigations have failed to detect a consistent specific pathogen

The course of the disease varies greatly some cases lasting for more than a decade with long periods of quiescence and other cases are fulminant ending fatally after a few months Death usually results from meningitis pneumonitis inanition or hemorrhage

Diagnosis During the early phases of midline granuloma it is important to rule out several specific nasal and facial conditions many of which are treatable These include leprosy syphilis yaws (gangosa) tuberculosis (lupus vulgaris) glanders leishmaniasis blastomycosis and coccidioidomycosis chromate poisoning lupus erythematosus also lymphomas mycosis fungoides and malignant tumors Midline granuloma is differentiated from Wegener s granulomatosis (p 1707) by the absence of generalized polyarteritis nodosa and glomerulonephritis Noma (p 881) is readily distinguished by its being largely restricted to children involving the cheeks and mouth but not the nose

Treatment No effective therapy for midline granuloma has yet been found The basic disease progresses despite administration of antibiotics or adrenocortical steroids A few early reports of benefit following radiotherapy have not been substantiated by further experience and nitrogen mustards have failed Radical surgical excision is no more effective than conservative debridement Various prostheses designed to maintain the integrity of the normal facial passages are helpful both functionally and cosmetically

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PART SEVEN

Diseases Associated with Reactions to Stress and to Antigenic Substances

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Section 1 Diseases Associated with Reactions to Stress and to Antigenic Substances

210 ALLERGIC DISEASES

Leighton E. Cluff

Definition Allergy or hypersensitivity in man designates the adverse reactions produced by exposure to a foreign substance (antigen) following an initial or sensitizing contact

Portier and Richet in 1902 coined the term *anaphylaxis* for the severe systemic reaction of dogs to reinoculation of foreign protein Four years later Roseman and Anderson showed conclusively that anaphylaxis is elicited only by the specific antigen to which an animal is sensitized The several local and systemic effects elicited by reexposure to antigen were referred to as *allergy* by Von Pirquet (1907) Jenner in 1801 observed acceleration of the local reaction to cowpox in immunized individuals and in 1890 Koch described sensitivity to tuberculin in patients with tuberculosis The relationship of pollen to hay fever and asthma was demonstrated by Blackley in 1865 and in 1903 Dunbar added animal dander and dusts to the list of antigens that commonly produce these disorders

Depending upon the character of the foreign substance that acts as antigen and the route of exposure to it allergy can appear in different forms In the *immediate* type of hypersensitivity the untoward reaction affects smooth muscle and blood vessels with resulting anaphylactic shock urticaria asthma hay fever or serum sickness (p 1697) Serum antibody to the antigen is usually demonstrable in this form of allergy and the hypersensitivity reaction often occurs after exposure via the respiratory tract Hypersensitivity of the *delayed* type is typified by the tuberculin reaction There is no association with serum antibody and exposure to antigen can result in damage to cells and tissues of many types This form of allergy is usually the result of bacterial infection or dermal exposure to antigenic substances

Asthma and hay fever are frequently familial and intracutaneous inoculation of the offending antigen often elicits an immediate wheal and erythema Allergy accompanied by these two features is commonly referred to as *atopic*

Etiology and Pathogenesis Contact with antigen is a prerequisite for development of allergy and hypersensitivity reactions are elicited only by reexposure to the antigen or some closely related substance The mechanisms involved in the interaction of antigen and antibody which leads to injurious effects however are poorly understood

The antigens in pollen dust and dander which are common causes of atopic allergy (manifested clinically as asthma) are probably proteins Specific antibodies associated with atopic allergy have features which distinguish them from antibodies of other types and are frequently referred to as *reagins* Reagins are not detectable by the usual in vitro immunologic procedures they are more resistant to heat than many other antibodies and they are firmly fixed at a local site of inoculation The presence of a reagin in serum correlates with the wheal and erythema elicited by intracutaneous injection of an antigen but bears no regular relationship to the presence or the severity of clinically significant allergic disease

Histamine is liberated by reactions of the immediate type and probably plays a role in producing some of the clinical manifestations of hypersensitivity Plasma proteolytic enzyme activity increases during certain hypersensitivity reactions but there is little evidence that it is responsible for the fundamental injurious effects The smooth muscle contraction characteristic of immediate hypersensitivity has led to the implication of acetylcholine in allergic reactions Changes in blood potassium adenosine serotonin heparin and many other substances have been described in allergic reactions but none of the biochemical abnormalities yet found has led to a satisfactory understanding of the mechanisms of hypersensitivity

Hypersensitivity itself is not inherited but the existence of a genetic predisposition to development of atopic allergy seems firmly established About 50 per cent of patients with hay fever or asthma will have a family history of allergic disease as opposed to only 15 per cent of the remaining population

Hay Fever

Hay fever is an allergic disease of man characterized by sneezing rhinorrhea itching of the eyes and lacrimation It is usually seasonal since sensitivity to air borne antigens particularly pollens is by far the most common cause Seasonal hay fever begins at an early age and is more frequent in

individuals from susceptible families Examination shows pale and edematous mucosa in the nose with secretion of large amounts of clear mucus

In *nonseasonal* hay fever there may be no family history of allergic disease There is often associated infection of the upper respiratory tract such as sinusitis Under this circumstance polyp formation in the nose is common

Eosinophils are abundant in nasal secretions and blood eosinophilia is common during atopic hay fever With coexistent respiratory infection however the secretions may predominantly contain neutrophils

Bronchial Asthma

Bronchial asthma is an allergic disease characterized by wheezing expiratory dyspnea and cough occurring spasmodically particularly after exposure to air borne antigens The respiratory manifestations are attributable to contraction of the bronchial and bronchiolar musculature edema of mucous membranes and accumulation of bronchial secretions In severe attacks hypoxia leads to cyanosis coma and rarely death Emphysema accompanies each paroxysm of acute asthma at first it is reversible but if the asthma occurs repeatedly it becomes intractable or permanent Paroxysms frequently begin at night Hyperexpansion of the thorax occurs and the diaphragm is low and relatively fixed Expiratory wheezes and rhonchi are heard *throughout the chest* The asthmatic attack may last for hours or days (status asthmaticus) With termination of the episode either spontaneously or after treatment the cough may become productive of large quantities of mucoid sputum containing small bronchial casts (Laennec s "perles and Curschmann s spirals) Anxiety is prominent during the asthmatic paroxysm Hay fever and urticaria sometimes precede development of asthma or occur simultaneously

Atopic asthma usually appears in young persons it is often seasonal and air borne antigens are almost always responsible Nonatopic asthma characteristically begins in older persons and is usually associated with chronic infection of the respiratory tract Air borne antigens do not seem to be the cause of this type and the disease has been termed "intrinsic asthma Intrinsic asthma is common in patients with chronic lung diseases of other types (see p 1387) Bronchial asthma is occasionally a principal manifestation of polyarteritis nodosa (p 1698)

Bronchial secretions in atopic asthma may contain eosinophils and blood eosinophilia is detected particularly when there are associated allergic skin reactions Radiologic examination of the chest during uncomplicated paroxysms usually shows depressed diaphragm and increased radiolucency of the lung The vital capacity is markedly reduced during an attack of asthma

Diagnosis Allergic reactions in the respiratory tract are identified entirely by their clinical characteristics

A history of allergic disease in the family—seasonal or recurrent attacks of nasal and bronchial symptoms or other allergic manifestations such as urticaria—is helpful in recognition of hay fever and bronchial asthma When hay fever and asthma occur during particular seasons or under certain environmental circumstances detection of the offending antigen is facilitated

The nasal mucous membrane in hay fever is pale and edematous in contrast to the reddened membrane observed in upper respiratory infection Pruritus about the eyes and nose is commoner in hay fever than in infection The presence of nasal polyps suggests coexistent infection and hay fever

Localized wheezing in the lungs is not a manifestation of bronchial asthma but is indicative of endobronchial disease such as foreign body aspiration neoplasm or stenosis In uncomplicated bronchial asthma examination of the lungs is usually normal between attacks Furthermore the wheezing and rhonchi occur almost exclusively in expiration whereas in bronchiectasis acute pulmonary *edema or pneumonia there are often inspiratory* rales as well "Cardiac asthma is occasionally indistinguishable from bronchial asthma The presence of inspiratory moist rales blood tinged sputum and cardiomegaly in cardiac asthma however is indicative of heart failure as the cause Poisoning with cholinergic drugs or insecticides may elicit manifestations of acute asthma which can be specifically relieved with atropine (p 778)

Skin Tests Intracutaneous inoculation of antigens is useful primarily for determining the reactivity of the patient to substances with which there has been environmental contact These tests are far less useful in specifying the antigens responsible for allergic disease Interpretation of skin reactions is dependent upon (1) the relationship of the allergic state to dermal reactivity (2) selection of the specific antigen for testing and (3) correlation of multiple hypersensitivities and the patient s disease Wheal and erythema reactions to a variety of antigens serve to designate a person as atopic or as having the propensity for developing an allergic illness upon exposure to the antigens Correlation of the skin test reaction with a historical analysis of allergic symptoms can facilitate determination of the agents responsible for symptoms Twenty five per cent of persons without allergic symptoms may have positive tests to common antigens the incidence is much higher in individuals with allergic disease In performing skin tests small doses of antigen should be used ini

tially Testing during an acute phase of hay fever or asthma is hazardous and should be avoided Treatment with adrenal cortical steroids will not interfere with the usual immediate" wheal and erythema reaction When it seems inadvisable to skin test a patient passive transfer of serum into the skin of a normal subject followed after a few hours by challenge at the same site with antigen may elicit wheal and erythema (Prausnitz Kustner reaction)

Therapy *Specific Treatment* Elimination of the offending antigen from the patients environment is the most successful means of preventing and treating allergic disease This is not always easy even when the antigen is known If it is determined that dander from dogs or cats is responsible these animals should be avoided A feather pillow may be replaced by one of foam rubber Air conditioning may alleviate symptoms produced by pollens The patient may be advised to move to a different location during periods when allergic symptoms arise Mechanical obstruction of the nares or tracheobronchial tree which may exaggerate the manifestations of hay fever or asthma should be corrected Complicating infection of the sinuses should be treated appropriately

Desensitization or *hyposensitization* of the patient is dependent upon recognition of the specific antigens which are the cause of an allergic disease Repeated inoculation of small amounts of antigen into sensitized persons or experimental animals is capable of suppressing reactivity to antigenic challenge The precise mechanisms involved are not well understood but under some circumstances this procedure results in production of a serum antibody (blocking) capable of inhibiting the reaction of antigen with reagins Subcutaneous inoculation of increasing amounts of antigen at intervals of a few days in dosage which does not elicit systemic or significant local discomfort may alleviate allergic symptoms Antigen can be given once or twice a week doubling each dose

If reaction occurs the dosage is kept the same or reduced after which increases can be given again An arbitrarily selected dosage level is maintained when satisfactory improvement appears Treatment by desensitization may be perennial seasonal or pre easonal Continued therapy throughout the year is probably preferable to discontinuous treatment In some instances the beneficial effects of desensitization may persist after the inoculations are discontinued but more often the allergic symptoms recur

Bacterial vaccines have been employed in desensitization of patients with nonatopic allergy Autogenous as well as standard vaccines are used The efficacy of this type of treatment however has not been fully established

Nonspecific Treatment HAY FEVER Hay fever is often alleviated by administration of antihistamines such as Benadryl or Pyribenzamine given in dosage of 50 mg three or four times each day As a rule however these agents lose their effectiveness after continued use Instillation into the nose of drugs such as Neo synephrine (¼ per cent) will shrink the edematous nasal mucosa but may if used repeatedly exaggerate and perpetuate the rhinitis Hydrocortisone and antihistamine nose drops also may provide temporary relief of the manifestations of hay fever Antibiotics should *not* be applied locally to the nares because they may induce sensitization Amphetamine inhalers can relieve an occluded nasal passage but continued use will cause persistence of nasal congestion *Systemic adrenal cortical steroids* frequently are effective in both atopic and nonatopic hay fever relieving symptoms and causing nasal polyps to disappear but long continued use carries the risk of side effects of steroid therapy (p 596) For temporary relief of acute symptoms however hydrocortisone in dosage of 200 mg per day can be very useful Prednisone may also be used but in about one fifth the dose of hydrocortisone (p 582)

In the usual case of hay fever nonspecific treatment with antihistamines should be used first If this is ineffective other therapy may be instituted particularly if the illness is disabling or severe

ASTHMA Treatment of acute asthma is most effective when begun soon after onset of the paroxysm Prompt relief can usually be achieved by subcutaneous injection of *epinephrine* 0 2 to 1 0 ml of a 1 1 000 solution repeated as needed but no oftener than every 30 min It is advisable to administer a sedative such as phenobarbital 60 to 90 mg with epinephrine to allay agitation and to relieve the anxiety accompanying an attack of asthma Epinephrine may become ineffective after repeated use It may be used in oil 1 0 ml of a 1 100 solution and injected intramuscularly for prolonged effect and may be vaporized as a 1 100 aqueous solution for inhalation Nebulized epinephrine analogues can be administered by the patient but if used repeatedly irritate the respiratory mucosa *Aminophylline* is an active bronchodilator which is beneficial in the person refractory to the action of epinephrine It may be used occasionally in preference to or in addition to epinephrine It may be given intravenously rectally or orally in decreasing order of effectiveness The dosage is 0 25 to 0 5 Gm When given intravenously the drug must be given slowly Rectal administration as a suppository or in water or oil is effective If the patient is cyanotic oxygen may be given but should be used intermittently particularly if chronic emphysema is present (p 1397) Ether administered rectally or as a general anesthetic may oc

casionally be successful in halting a severe attack of asthma *Adrenal cortical steroids* may be given in severe or intractable paroxysms in the same dosage as described for hay fever but are not always effective If an asthmatic episode is unresponsive to the use of epinephrine and aminophylline or recurs promptly it may be advisable to give a continuous intravenous infusion of 1 liter 5 per cent glucose containing 0 25 to 0 5 Gm aminophylline over 1 to 2 hr Morphine should never be given to the patient with acute asthma but *Demerol* 50 to 100 mg is useful as a sedative and antispasmodic Hydration should be maintained to prevent inspissation of bronchial mucus If inspissation of bronchial secretion develops bronchoscopy can be valuable Intractable asthma is commonly complicated by pulmonary infection and appropriate treatment may be beneficial Antibiotic therapy however must not be indiscriminate

Prophylactic management of the asthmatic patient involves the use of drugs with which the patient can abort paroxysms and institution of measures directed to improve general health Oral *ephedrine* (25 to 50 mg) and phenobarbital (30 to 60 mg) are commonly used to abort an asthmatic attack This drug combination is less effective in management of a fully developed asthmatic paroxysm *Aminophylline* (0 25 to 0 5 Gm) may be added to the combination of ephedrine and phenobarbital During a period of time when the patient is most likely to develop asthma ephedrine phenobarbital and aminophylline (APE) may be given three or four times each day When the patient is awakened at night by an attack of asthma aminophylline suppositories at bedtime are frequently effective in preventing the episodes Administration of *meprobamate* and other tranquilizing drugs has had some vogue in management of asthma possibly with a measure of success Similarly continued small doses of barbiturates have been used to allay the chronic anxiety occasionally displayed by some patients Psychotherapy has had little applicability

Smoking is undesirable in asthmatics as are obesity excessive exertion fatigue and dietary indiscretion

Atopic or seasonal asthma is most amenable to desensitization in contrast to nonatopic asthma Nonatopic asthma occasionally necessitates continuous administration of adrenal cortical steroids in order to suppress disabling symptoms Continuous administration of antibiotics to patients with nonatopic or intrinsic asthma is usually ineffective and unwise and will not prevent respiratory infection

Prognosis Hay fever is a benign disease principally uncomfortable and annoying to the afflicted person Bronchial asthma is also usually a benign disease and rarely causes death The only important prognostic implication of asthma is its causal relationship to obstructive emphysema which may produce pulmonary insufficiency cor pulmonale and cardiac failure The effective management of asthma however significantly lessens this possibility

Allergic Dermatitis

There are many dermatologic manifestations of allergic reactions including urticaria angioedema contact dermatitis erythematous rashes and eczematous eruptions The specific erythemas are discussed in the section beginning on page 1709

The hypersensitivity reactions responsible for allergic dermatitis may be of the immediate or the delayed type Contact dermatitis occurring after exposure of the skin to a sensitizing substance is accounted for by delayed hypersensitivity Urticaria angioedema and probably most erythematous eruptions are attributed to immediate hypersensitivity and usually develop after inhalation ingestion or parenteral inoculation of the antigen Allergic dermatitis due to delayed hypersensitivity is usually identified by means of a *patch* test with a resulting eczematous eruption at the site of application of antigen The immediate hypersensitivity responsible for allergic dermatitis can occasionally be determined by development of wheal and *erythema at the site of intradermal inoculation* of antigen

Contact dermatitis is probably the commonest type of allergic skin disease Many drugs chemicals plants and foods may induce such reactions The lesion produced varies in its clinical features but usually appears only in areas exposed to the offending substances As a rule the involved skin is eczematous and reddened There may or may not be pruritus Chronic involvement and scarification by scratching may cause lichenification of the skin

Diffuse allergic *eczematous dermatitis* occurs most often in young persons and is commonly a hypersensitivity reaction to foods or other ingested substances The principal lesions appear symmetrically in the antecubital popliteal neck or face regions Pruritus is usually severe and lichenification or chronic irritation of the skin may result from scratching *Neurodermatitis in adults* has similar distribution and clinical characteristics but is often attributed to stressful life situations and emotional disturbance

Identification and elimination of the offending antigen are the only satisfactory means of treatment Local or systemic administration of adrenal cortical steroids will usually suppress the dermatitis but recurrence is the rule when this treatment is discontinued if the antigen has not been eliminated

Other forms of treatment such as the application of soothing lotions are usually not very beneficial and furthermore may result in development of hypersensitivity reaction to the therapeutic agent

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211 ALLERGIC REACTIONS TO DRUGS

Leighton E Cluff

The increase in allergy to drugs parallels the growing use of pharmaceutic agents in the management of disease With the continual introduction of new drugs this problem can be expected to become even more serious

Definition Classification of a drug reaction is not always easy but undesired responses to therapeutic agents have certain specific features which facilitate their characterization Nearly all drugs can elicit pharmacologic effects other than those for which they are administered and when these appear they are referred to as *side effects* or *toxic effects* Some patients exhibit unusual susceptibility to the pharmacologic actions of a drug and are said to have an *idiosyncrasy* In addition reactions not explained by the pharmacologic properties of a drug and therefore indicative of altered reactivity of the patient are termed *allergic* Side effects as a rule are intensified by increasing dosage or cumulative action and readministration is not associated with increased reactivity of the patient For example nausea hyperpnea and tinnitus in a person given large doses of aspirin are side effects and reduction in dosage will usually alleviate the situation The occasional patient who displays these symptoms after taking a small amount of aspirin has an idiosyncrasy to the drug However if ingestion of aspirin is followed by bronchial asthma or urticaria reactions not explainable by the drugs pharmacologic action the patient is allergic to it This type of reaction is likely to be associated with symptoms commonly ascribed to hypersensitivity (rash asthma pruritus arthritis fever leukopenia etc) frequently recurs promptly on readministration of the drug and is not closely dependent on dosage or cumulative action

The clinical importance of differentiating side effects idiosyncrasy and allergy relates of course to the hazard of readministration of a drug or its probable safety in lower dosage

Etiology Allergy is believed to result from the formation of specific antibody to a drug However most pharmacologic agents are incapable of stimulating antibody formation by themselves and it is thought that the actual antigen is a conjugate of the drug with serum or tissue proteins Under such circumstances the drug would act as a hapten nonantigenic by itself but conferring specific antigenicity to the protein and capable of combining with the antibody formed in response to the drug protein conjugate In support of this concept are the many demonstrations of binding of drugs by body proteins as well as experimental evidence that the ability of chemical compounds to elicit hypersensitivity can be correlated with their affinities for proteins

In the majority of instances the usual techniques for demonstrating antibody yield negative findings in drug allergy Precipitation hemagglutination or complement fixation tests with a patient s serum may be negative and direct intradermal or passive transfer tests of the Prausnitz Kustner type are often unrevealing Such results however are more indicative of the inadequacy of present methods of testing than an argument against an immunologic basis for hypersensitivity to drugs The lack of consistently effective testing methods is of course a great handicap to clinical investigations of drug reactions

Manifestations The commonest manifestations of allergy to drugs are no different from hypersensitivity reactions of other types and include rashes asthma and the symptoms of serum sickness (see Table 99) These are easily recognized clinically as allergic in origin Other features of drug allergy are sometimes less easily characterized however The tabulation see p 1164 of this chapter of common drugs and reactions which they may elicit includes some effects that may not be allergic at all A few examples of allergic drug reactions will illustrate the variations seen with different pharmacologic agents

Skin Morbilliform urticarial and maculopapular rashes are the most common skin reactions but many others are observed including vesicular bullous exfoliative eczematous and purpuric eruptions Pruritus is frequent Although *the type of* skin lesion usually will not aid in identifying the

Table 99 COMMON DRUG REACTIONS

Drug	BLOOD								SKIN													NEUROLOGIC							GASTRO-INTESTINAL					
	Anemia	Agranulocytosis	Eosinophilia	Hemolysis	Thrombopenia	Aplastic anemia	Lymphocytosis	Leukocytosis	Rash	Bullae and vesicles	Exfoliation	Urticaria	Erythema multiforme	Eczema	Purpura	Fixed eruption	Photosensitization	Contact dermatitis	Fever	Serum sickness (anaphylaxis, asthma, etc.)	Jaundice	Delirium	Orthostatic hypotension	Peripheral neuritis	VIII nerve palsy	Paresthesia	Parkinsonism	Ascending paralysis	Nausea, vomiting	Abdominal pain	Diarrhea	Renal disorders	Periarteritis nodosa	Systemic lupus erythematosus
Acetanilid	0	0		+	0	0		+	+			+							+															
Antipyrine									+							+			+	+														
Aminopyrine		+							+							+			+	+														
Amphetamine (Benzedrine)									+													+												
Antihistamines		+							+										+															
Arsenicals		+		+	+	+			+	+	+				+				+	+	+	+		+								+		
Atropine								+	+		+								+	+		+												
Bacitracin																																+		
BAL (dimercaprol)									+									+	+															
Banthine									+		+																							
Barbiturates	+	0							+	+	+	+			+				+			+												
Bismuth									+		+								+		+			+							+	+		
Boric acid									+									+											+					
Bromides										+			+						+			+							+			+		
Carbarsone									+		+								+			+												
Chloral hydrate									+			+			+														+			+		
Chloramphenicol		+			+	+			+											+	+								+					
Chloroquine									+																				+					
Chlorpromazine (Thorazine)																																		
Cocaine (derivatives)												+					+	+									+		+	+				
C[illegible]d														+					+	+														
Col[illegible]											+																		+					
DDT		+																										+	+		+	+		
Dextran									+																								+	
Diethylstilbestrol												+								+														
Digitalis					+				+																				+					
Dilantin			+				+		+			+							0			+		+		+								
Diodoquin			+					+	+		+		+						+		+			+										
L[illegible]et									+	+									+													+	+	
[illegible]												+		+	+								+											

Γι ledn																		+								+			+					
Ergot alk l ds																																		
F m ld l 3d														+				+				+								+	+		+
~ d		+			+				+		+																							
H ȝ rı												+							+	+						+			+		+			+
Hydr l	+					+			+			+							+															
I (									+			+																			+		+	
Iod des										+	+				+				+	+														
Ipro u d																					+	+	+											
Isot d		+													+																			
Kl									+																									
Li e t t												+							+	+														
M d l d									+			+													+									
M pe di (D n l)																			+															
M reu ials		+							+	+	+	+							+	+									+			+		
Mes t		+		+	+	+															+													
Methyltestost e																					+													
Morph												+						+		+														
Ne my n																									+									
N rv l		+	+				+		+		+								+	+														
Nitr f t																																		
(F r da t)				+	†														+										+					
Par				+	†																													
p-A os l yl d		0							+										+															
P llın	0	0	0	0	0	0			+	+	+	+						+	+	+		+											+	
Pl lpl th l									+	+						+																		
Pl		+				+			+		+								+		+								+			+		
Ph yll ta e																																		
(B t t)		+			+	+			+										+															
P a (A t y r)												+																						
P lymy																																+		
Pr maq																					+	+							+	+				
Pr ter ec d (B d)									+																				+					
F u m d																																		
(Pro estyl)		+							+			+					+		+	+		+							+		+			
Q (At tr)	+								+		+			+				+	+		+	+							+					
Q i					+				+		+								+	+		+			+				+	+	+			
Q n		+		+					+										+	+					+				+			+		
R lfi												+																	+		+			
l yl tes (a, r n)		0			+				+	+	+	+		+	+				+	+					+				+					
~ p l n									+		+								+	+		+												
Str y t			+		+	+			+		+	+						+	+	+		+			+	+			+		+			
~ lf m des		+	+	+	+	+			+	+	+	+	+		+		+		+	+	+	+		+								+	+	
T (ra y) (d a																																		
t es)									+		+	+					+				+								+		+			
Th c y t	+	+							+		+				+				+		+	+		+					+		+	+		
Th io l									+										+															
T m th d e																																		
(T dio e)					+	+			+		+		+								+											+		
V t i lk ds																						+				+								

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causative drug there are certain skin reactions which are somewhat specific Erythema multiforme or nodosum is particularly seen in allergy to Dilantin bromides iodides trimethadione and sulfonamides Fixed drug eruptions are most frequently due to amidopyrine phenolphthalein or Atabrine Photosensitization during drug therapy *occurs characteristically with chlorpromazine* phenothiazine sulfonamides and tetracycline derivatives

Fever Fever may be an isolated manifestation of drug allergy and at least 35 pharmaceuticals in common use can produce a febrile reaction including most antibiotics and chemotherapeutic agents However the tetracycline derivatives are uncommon causes of drug fever and digitalis has rarely if ever been incriminated as the cause of a pyrogenic reaction Elevation of temperature can appear abruptly after initiation of treatment or develop in a stepwise fashion during or after the second week of drug administration Drug fever is often associated with chills and constitutional symptoms Discontinuance of therapy usually results in defervescence within a very few hours although several days may be required for return of temperature to normal

Blood Changes in the formed elements of the blood are rather common during drug allergy and may have no specificity Some drugs have been found to have limited or no effects on the blood while others produce specific abnormalities For example penicillin has never been incriminated as a cause of serious hematologic abnormalities In therapeutic doses acetanilid is probably not a cause of *anemia agranulocytosis thrombocytopenia* or *aplastic anemia* in high dosage however it may produce *leukocytosis methemoglobinemia* and *acute hemolysis* Methemoglobinemia also occurs with antipyrine nitrites sulfonamides primaquine and pamaquine but this reaction is probably not allergic in origin Barbiturates salicylates and para aminosalicylic acid rarely if ever produce agranulocytosis Eosinophilia can accompany allergic reactions of many types but occurs with such frequency as an isolated finding during therapy with streptomycin or nirvanol that it has no significance in these instances *Lymphocytosis* is common in patients receiving Dilantin and nirvanol but *polymorphonuclear leukocytosis may be found in individuals taking* Dilantin or atropine Recent studies of the erythrocyte abnormality responsible for the acute hemolytic anemia induced by primaquine in certain individuals indicates that what was thought to be drug allergy is actually a genetically determined idiosyncrasy (p 1184) *Jaundice* and *acquired hemolytic anemia* due to pharmaceutic agents are discussed elsewhere (p 1181)

Nervous System A variety of neurologic manifestations may appear during drug therapy but in the majority of instances there is little evidence to incriminate allergy as a cause The commonest reaction by far is delirium seen particularly with digitalis atropine thiocyanates and sedatives Other drugs which produce adverse effects upon the nervous system (ranging from paresthesias and peripheral neuritis to deafness) are streptomycin hydralazine chlorpromazine Diamox isoniazid polymyxin and neomycin

Others Nausea vomiting and diarrhea are exceedingly common drug reactions In addition abdominal pain in the absence of other symptoms may be produced by quinidine chlorpromazine and primaquine Albuminuria and cylindruria occur particularly with heavy metals bacitracin and polymyxin However Dilantin chloral hydrate sulfonamides trimethadione Phenurone colchicine and thiocyanate occasionally produce renal dysfunction probably by direct toxic action Hypersensitivity to sulfonamides has resulted in acute hemorrhagic nephritis

Histologic lesions indistinguishable from those of periarteritis nodosa have been found in the tissues of patients who have experienced allergic reactions to iodides Dilantin sulfonamides and penicillin (p 1698) Manifestations of systemic lupus erythematosus have appeared during therapy with gold or hydralazine (p 1700)

Anaphylaxis may follow the parenteral administration of a variety of drugs but the agent most seriously incriminated at present is penicillin Development of anaphylaxis has been reported after oral ingestion of the drug but this is exceedingly rare

The incidence of drug allergy is not high and is particularly related to the frequency with which a pharmacologic agent is used clinically For this reason probably these reactions are now often observed with antibiotics However the incidence of allergic reaction also varies with the agent and with some drugs may be as high as 10 per cent

Treatment and Prophylaxis Allergic reactions to drugs usually subside promptly when the agent is discontinued For reasons that are not understood however the reaction occasionally persists for prolonged periods in spite of withdrawal recurrent urticaria for many months after a penicillin reaction is a common example The management of serum sickness is described elsewhere (p 1697) In the event of persistent or severe manifestations of drug allergy the use of adrenocortical steroids is indicated Adrenal steroids antihistamines and adrenalin are usually ineffective in alleviating reactions due to idiosyncrasy or side effects of a drug Reactions of this type are best managed by adminis

tration of other drugs with appropriate pharmacologic actions i e sedatives for excitability stimulants for depression etc and by withdrawal of the offending drug

Although it is not possible to predict the occurrence of drug allergy in a patient the fact that hypersensitivity to drugs may be commoner in individuals with other allergic reactions makes it reasonable to inquire about this before initiation of treatment with any agent A specific history of hypersensitivity to a given drug contraindicates its readministration unless the clinical situation is serious In a number of instances where it has been judged necessary to prescribe a drug to which a patient is known to be allergic (e g penicillin for bacterial endocarditis) the concomitant administration of adrenal steroids has completely suppressed the manifestations of hypersensitivity

Although it is commonly said that sensitivity to a drug will subside if its administration is continued this is not a regular occurrence and should not be accepted as a basis for further therapy with the incriminated agent

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PART EIGHT

Diseases of Organ Systems

Section 1 The Hematopoietic System

M M Wintrobe

The hematopoietic system includes the circulating blood the bone marrow the spleen and the lymph nodes supplemented by the reticuloendothelial cells scattered about the body The liver through the presence there of reticuloendothelial cells as well as by reason of other functions is also intimately concerned in blood formation and destruction Since the function of the red corpuscles is to hold in nondiffusible form the pigment hemoglobin essential for the transport of oxygen any alteration in the quantity of red corpuscles or in their hemoglobin content affects the function of all the organs of the body An important function of the leukocytes is to take part in the reaction to injury particularly in the defense against infection The blood platelets are concerned in maintaining the integrity of the vascular endothelium and in the clotting of blood The blood plasma which carries these three types of corpuscles is also the medium for the transport of many substances concerned in the metabolism of the organism

Since the blood and its constituents are so intimately related to the body as a whole much will be found concerning the blood in various chapters *in this book and particularly in those in Part Two* In regard to the red blood corpuscles attention should be called especially to Chap 12 (Hypoxia Cyanosis and Polycythemia) and to Chap 22 (Pallor and Anemia) In the latter the synthesis and the destruction of hemoglobin and the classification and management of anemia are considered as well as the pathogenesis symptomatology and methods of study of a patient with anemia The platelets the phenomenon of coagulation and the various ways in which bleeding is produced receive attention in Chap 23 (Bleeding)

In the present section disorders of the hematopoietic system will be considered It is evident that such disorders make themselves known in a variety of ways These may be such that discovering their cause may tax the acumen of even the most discerning physician In the main however they are characterized in part or whole by symptoms and signs such as pallor cyanosis jaundice bleeding or enlargement of the lymph nodes or spleen A thorough understanding of these manifestations of disease is a prerequisite to the correct differentiation as well as the effective treatment of the disorders of the hematopoietic system

The *approach* to the patient suspected of having a hematopoietic disorder is discussed therefore in Part Two under headings such as Bleeding Enlargement of Lymph Nodes and Spleen Anoxia Cyanosis and Polycythemia Although in the subsequent pages descriptions of the various recognized disorders of the hematopoietic system will be found and their treatment discussed it is urged that the reader confronted with a problem for example of anemia first study Chap 22 because he will find there a discussion of anemias in general and he will thereby make his way more readily through the pages that follow or for that matter through other sections in this textbook The same is true in principle if the problem is one of bleeding or cyanosis or splenomegaly

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M M Wintrobe

POSTHEMORRHAGIC ANEMIA

Anemia resulting from blood loss may have developed suddenly because of the rapid loss of a large quantity of blood or it may have come about very gradually over a period of many months or even years Obviously there are also many possible variations between these two extremes The causes of posthemorrhagic anemia are numerous and the manifestations differ widely the latter depending in part on the nature of the underlying disorder and in part on the quantity and speed of the blood loss It is convenient to consider acute and chronic posthemorrhagic anemias separately because their *manifestations and in certain respects their treatment* differ so greatly It should be realized however that these two syndromes represent two extremes depending in the main on the same underlying defect and that in practice variations will be encountered which represent all stages between these extremes

Acute Posthemorrhagic Anemia

Etiology Trauma the rupture of a peptic ulcer or of an ectopic pregnancy and bleeding in connection with hemophilia or purpura hemorrhagica

are examples of the widely varied possible causes of acute blood loss They indicate that the blood loss may be external and recognizable at once or internal and consequently sometimes not readily discovered

Symptomatology The rapid loss of blood leads to reduction in blood volume and the clinical manifestations are mainly circulatory If the blood loss is great acute posthemorrhagic shock develops (see Chap 14) If the hemorrhage is visible to the patient whether the amount of blood lost is great or small symptoms may arise from the psychic effect of such bleeding Generally speaking symptoms are likely to appear sooner and are more pronounced in relation to the amount of blood lost when the bleeding is external than when it is not recognizable by the patient The manifestations of anemia in general have been discussed already (p 202) In addition the symptoms of the underlying disorder may be present as well

Blood Picture Polymorphonuclear leukocytosis with the appearance of immature forms (shift to the left) is the first discernible change An increase in platelets often takes place as well The anemia may not be apparent at once since at first plasma is lost as well as red corpuscles so that the ratio of cells to plasma remains the same As fluid is drawn from the tissues to restore the blood volume anemia becomes apparent This is normocytic at first Blood loss in an otherwise healthy organism however profoundly stimulates the bone marrow This becomes hyperplastic and immature corpuscles are liberated in larger numbers than usual Reticulocytosis ensues polychromatophilia is found and even nucleated red corpuscles find their way into the blood At this stage the anemia may be macrocytic since the immature cells are larger than the older forms Reticulocytes begin to appear within 48 hr following a brisk hemorrhage and may continue to increase for several more days A persistent reticulocytosis forming a plateaulike curve suggests that bleeding is continuing for cessation of hemorrhage is marked by quick restoration of physiologic balance with rapid regression of the signs of stimulated hematopoiesis If the iron stores of the body are good and the blood loss has not been extreme iron deficiency does not occur and hypochromia is slight or absent When the drain on iron is greater than can be readily replenished iron deficiency begins

When the acute hemorrhage is internal destruction of the blood and absorption of the products may lead to an increased excretion of urobilinogen in the urine and stools and rarely even slight bilirubinemia may be found Bowel hemorrhage is often associated with an increase in the blood urea nitrogen level

Diagnosis When acute hemorrhage is not evident such signs as pallor faintness restlessness sweating and palpitation should lead to a search for hemorrhage If the subject is recumbent much blood may be lost before these signs appear They can be brought out by tilting the patient to the erect position Late signs of acute blood loss are air hunger thirst and a falling blood pressure

Prognosis The amount and rapidity of the blood loss the acuteness of the physician in discovering it the availability of blood for transfusion and the accessibility of the site of bleeding are the important considerations

Treatment Stopping of the hemorrhage and restoration of the blood volume to normal preferably by transfusions of whole blood otherwise by administration of plasma or other fluids are the essentials Speed in restoration of blood volume is more important than whether plasma or whole blood is used If the blood loss has been great and the blood volume is profoundly reduced multiple portals should be used for administration of blood and even intraarterial administration may be advisable Fluids by mouth (unless the bleeding is from the upper portion of the alimentary tract) and by hypodermoclysis are valuable adjuncts as are rest and quiet induced by morphine if necessary Following the acute phase a good diet containing meat fruit and vegetables affords the proteins and vitamins needed for erythropoiesis Iron can be given in the form of ferrous sulfate (0 2 to 0 4 Gm t i d) but is not needed in previously normal individuals unless blood loss has been great

Chronic Posthemorrhagic Anemia

This refers to that state in which blood loss has produced a chronic anemia and a deficiency of substances necessary for blood formation has developed Although the factors essential for erythropoiesis are many the chief deficiency resulting from chronic blood loss is that of iron The manifestations of chronic posthemorrhagic anemia can therefore be discussed in the section which follows

IRON DEFICIENCY ANEMIA (Hypochromic Microcytic Anemia Idiopathic Chronic or Nutritional Hypochromic Anemia Chlorosis Chlorotic Anemia Chloranemia)

Etiology Iron is normally obtained by digestion of food and is absorbed chiefly in the upper portion of the gastrointestinal tract This is aided by the acid secretion of the stomach The absorbed iron is utilized for hemoglobin formation as well as for the production of myoglobin and other enzymes Normally a large reserve is stored in the liver spleen and other tissues The total iron store in man which is available for blood formation has been estimated to amount to 1 2 or 1 5 Gm Once absorbed iron is conserved tenaciously The amount

lost per day by the normal adult male has been estimated as approximately 1 mg

Any circumstance which leads to a greater demand on the iron stores of the body than can be supplied results in iron deficiency In logical order the possible factors leading to iron deficiency are (1) insufficient iron in the diet (2) impaired absorption (3) increased requirements and (4) loss of blood Of these the *chronic loss of blood* by hemorrhage is by far the most common factor in the development of iron deficiency Excessive menstruation and occult bleeding from the gastrointestinal tract (peptic ulcer esophageal varices hookworm infection etc) are the most common types of bleeding which may result in iron deficiency since the former is but an exaggeration of a physiologic process and may thus receive little attention while the latter may pass unnoticed for a long time

Impaired absorption of iron is rarely an important factor in the development of iron deficiency even though various influences favor or inhibit the availability and absorption of iron Thus a high level of calcium in the diet diminishes the formation of insoluble iron phosphates and favors absorption of iron but excess calcium inhibits iron assimilation Ascorbic acid favors iron assimilation probably by promoting the reduction of ferric iron in food to the ferrous form Although the gastric hydrochloric acid favors ionization and thus absorption many persons are encountered in whom achlorhydria has existed for years without iron deficiency developing Chronic diarrhea however is of more importance Certainly iron deficiency may be encountered in sprue

Deficiency of iron in the diet alone is rarely a cause of iron deficiency except in infants receiving a milk diet exclusively and occasionally in elderly people who although they have had no blood loss for many years have depleted their stores by consuming a diet very low in iron

In children and adolescents the iron needs for *growth* are very important and it is largely because of the demands made by the ever-expanding blood volume that infants receiving an unsupplemented diet of milk develop iron deficiency In older children and adolescents poverty or faulty habits may contribute to the mounting deficiency by causing consumption of a diet too low in iron to supply the needs In girls the menstrual loss of blood accentuates this deficiency Normal menstruation results in an average loss of 0 5 to 1 0 mg iron per day *Chlorosis* the green sickness" of the last century and before was probably no more than iron deficiency in adolescent girls in whom low dietary iron was insufficient to meet the needs In adult women the iron requirement during *pregnancy* and *lactation* are factors which may lead to the development of iron deficiency anemia Pregnancy results in a net deficit of iron of approximately 1 mg per day lactation about 0 5 mg per day Often these circumstances are superimposed on a state of gradually increasing iron depletion which may have had its beginning in adolescence The ultimate combined effect of chronic loss of blood increased demands and faulty diet may not become clearly manifest until thirty to forty five years of age the period in which the *chronic hypochromic anemia* of women is most often seen It is of interest that in such individuals certain *constitutional features* similar to those encountered in pernicious anemia may be observed such as early graying of the hair and achlorhydria

Since so little iron is excreted normally iron deficiency develops *in the adult male* only from loss of blood or from dietary deficiency or impaired absorption which has existed over a period of many years In the male ulcerative lesions in the gastrointestinal tract are by far the most likely causes of long continued undetected loss of blood

Symptomatology The symptoms are those common to all chronic anemias and may include a variety of vague gastrointestinal complaints such as anorexia capricious appetite or heartburn and more rarely sore tongue sore mouth and dysphagia (Plummer Vinson syndrome) or palpitation dyspnea and edema about the ankles or neuralgic pains vasomotor disturbances or numbness and tingling Menstrual disturbances are common—menorrhagia irregularity of flow or even phases of amenorrhea

A tired lifeless appearance pallor inelastic and often dry and wrinkled skin sometimes with a brownish hue dry and often scanty hair and blue scleras are found in cases of long standing In many some degree of papillary atrophy of the tongue slight cardiac enlargement functional systolic murmurs and a palpable spleen are discernible When the deficiency is severe the nails may be flattened longitudinally ridged or even concave (koilonychia) and may break easily The sore tongue dysphagia and changes in the hair nails and skin may occur in iron deficiency prior to the development of anemia

Blood Picture A good blood smear will reveal thin pale red corpuscles poorly filled with hemoglobin In some cases these may be mere rings Tiny microcytes target like cells elliptic cells and bizarre poikilocytes are also found as well as a certain proportion of normally filled corpuscles The anemia is hypochromic and microcytic Only in this type of anemia is a substantially reduced mean corpuscular hemoglobin concentration (MCHC) encountered (less than 30 per cent) This hypochromia is more significant than the microcytosis although the latter may be extreme (mean corpuscular volume 55 to 75 cuμ) The

red corpuscle count may be normal or nearly so or even greater than normal while the hemoglobin and volume of packed red corpuscles are greatly reduced The leukocyte count is normal or slightly reduced and a slight thrombocytopenia may exist

The *bone marrow* is hyperplastic and contains an excessive number of normoblasts

Diagnosis The symptoms are naturally varied since iron deficiency may result from a large variety of causes When iron depletion is only moderate in degree the changes in the blood may not be striking In more advanced cases adequate examination of the blood should make it clear that hypochromic microcytic anemia exists This type of anemia is most often due to lack of iron Experimentally a similar anemia is observed in copper and in pyridoxine deficiency but in man such deficiencies are exceedingly rare if they occur at all Metabolic disorders involving these substances have been described however Thus there is a syndrome in infants and young children in which low serum copper values and hypoproteinemia accompany a hypochromic microcytic anemia which responds to iron therapy Again an adult man has been described whose refractory hypochromic anemia responded to pyridoxine Also in two men hypochromic anemia together with hyperferremia has been described which failed to respond to all therapeutic measures other than the oral administration of a crude liquid extract of liver Again under the title of *hereditary sex linked (?) anemia* a form of hypochromic microcytic anemia accompanied by marked poikilocytosis and splenomegaly was described as affecting males though transmitted only by females This anemia failed to respond to any form of therapy and must be exceedingly rare as are the other examples of hypochromic microcytic anemia just mentioned The only form of anemia of this type which is not extremely rare and which may be mistaken for that due to iron deficiency is thalassemia (p 1192) Consequently the discovery of hypochromic microcytic anemia usually calls for a search for causes of iron deficiency and in particular requires a thorough search for sources of blood loss

Prognosis This is excellent in so far as the possibility of relieving the anemia is concerned The prognosis otherwise depends on the character of the contributory causes

Treatment Only in iron deficiency anemia is iron therapy of value Here the administration of *ferrous sulfate* or *ferrous gluconate* is followed by a reticulocyte response and subsequently rapid red corpuscle regeneration occurs Gastric irritation is less likely to occur if tablets of 0 2 to 0 3 Gm are taken on a full stomach To allow the patient to become accustomed to it at first a total of 0 4 to 0 6 Gm is given per day but this may be increased to 1 or 1 2 Gm In addition to iron therapy a good diet containing meat fruit and vegetables is to be recommended and any underlying or associated disorder should be corrected Transfusion of blood is rarely if ever needed even in the most anemic and free hydrochloric acid is not required even if achlorhydria is present Failure to respond to oral iron therapy necessitating intravenous administration has been described but is exceedingly rare

MACROCYTIC ANEMIAS

Elucidation of the pathogenesis of pernicious anemia even though still incomplete has made it clear that there are a number of closely related disorders which have in common a characteristic type of anemia megaloblastic hyperplasia of the bone marrow and the capacity to respond to liver therapy yeast pteroylglutamic acid vitamin B_{12} or related substances These conditions the *megaloblastic macrocytic anemias* must be differentiated from those instances of macrocytosis which represent increases in mean corpuscular volume from other causes usually from the presence in the circulation of a relatively large number of immature red corpuscles appearing in response to such hematopoietic stimulants as severe hemorrhage or acute blood destruction (Table 100) In this second type of macrocytic anemia the bone marrow is not megaloblastic and liver vitamin B_{12} or folic acid therapy has no value The clinical differentiation is usually easy

Pernicious Anemia (Addisonian Pernicious Anemia Addison s or Biermer s Anemia Primary Anemia)

Definition Pernicious anemia is a chronic disorder characterized by macrocytic anemia megaloblastic hyperplasia of the bone marrow gastric achlorhydria and often glossitis and changes in the nervous system This disorder appears to be the consequence of a permanent gastric secretory defect associated with atrophy which results in a deficiency in the body of a substance derived from food The deficiency can be corrected by supplying a substance present in certain liver extracts which appears to be identical with vitamin B_{12}

History Although the disorder was described at least as early as 1823 by Combe it was the picture given by Thomas Addison in 1855 and the comprehensive description by Biermer in 1872 which drew attention to this ultimately fatal (therefore "pernicious) anemia *The discovery of the value* of liver therapy by Minot and Murphy in 1926 and the elucidation of the role of the stomach in the pathogenesis of the disorder by Castle in 1929

Table 100 CLASSIFICATION OF MACROCYTIC ANEMIAS

I Megaloblastic macrocytic anemias

A Conditions responding to administration of purified liver extract vitamin B_{12} or pteroylglutamic acid (PGA)

Disorder	*Probable pathogenesis*
1 Pernicious anemia	Lack of gastric (intrinsic) factor
2 Sprue idiopathic steatorrhea	Impaired absorption
3 Resection of small intestine	Diversion of PGA and B_{12} from host
4 Nontropical nutritional macrocytic anemia	Dietary deficiency
5 Tropical macrocytic anemia	Dietary deficiency
6 Macrocytic anemia with *Diphyllobothrium* infestation	Assimilation of vitamin B_{12} by worm thus depriving host
B Conditions apparently responding only or most often to administration of PGA rather than vitamin B_{12}	
7 Megaloblastic anemia of infancy	PGA deficiency associated with dietary deficiency of ascorbic acid
8 Megaloblastic anemia of pregnancy	Dietary deficiency? Increased requirements for fetus? Presence of inhibitor or antagonist?
9 Refractory megaloblastic anemia	Impaired metabolism of PGA?
10 Achrestic anemia	Impaired metabolism of PGA?
II Nonmegaloblastic macrocytic anemias	
Some instance of macrocytosis due to	
1 Acute posthemorrhagic anemia	Presence in blood of many immature erythrocytes
2 Hemolytic anemia	Presence in blood of many immature erythrocytes
3 Aplastic anemia	Unknown
4 Hypothyroidism	Unknown
5 Liver disease	Unknown

Pernicious anemia is distinguished from the other conditions listed in that achlorhydria is always present and neurologic changes may occur

N B In practice the most common cause of macrocytic anemia is laboratory error and this is most often due to errors in red corpuscle counting

completely changed the prognosis of the condition and profoundly stimulated hematologic research in general

Etiology This disorder is very rare in persons under the age of thirty and is encountered much more frequently in light haired blue eyed individuals than in the darker races or in Orientals It is seen especially in natives of the British Isles the Scandinavian countries and other more northern regions as well as in their offspring in other parts of the world Nevertheless although less common pernicious anemia is seen in Negroes

A familial incidence is not unusual Those affected often have turned gray prematurely and they may have broad faces and large bony frames Males and females are affected about equally

That a gastric secretory defect is a fundamental factor in the pathogenesis of pernicious anemia was suspected almost as early as the disease was recognized It was shown later that absence of hydrochloric acid in the gastric secretion and a greatly reduced total gastric secretion (achylia) precede the development of the anemia by many years It has also been shown that such achylia is a defect which persists in spite of successful antianemic therapy Castle demonstrated that the significant abnormality in gastric secretion is not lack of hydrochloric acid but absence of an intrinsic factor which normally acts upon an extrinsic factor derived from food The material so produced was regarded as leading to the formation of a substance stored in the liver without which normal hematopoiesis cannot take place The gastric factor is thermolabile It seems to be contained in or adsorbed to the glandular mucoprotein of the stomach The thermostable food factor is present in meat eggs cereals and other natural sources of the vitamin B complex and is also present in liver Desiccated hog s stomach given orally has the same hematopoietic effect in pernicious anemia as liver and its effectiveness was assumed to be due to the interaction of the intrinsic and extrinsic factors in gastric tissue

The discovery of vitamin B_{1} (cyanocobalamin) a red pigment containing cobalt and the demonstration of its therapeutic effectiveness in pernicious anemia on parenteral administration in amounts as small as 1 μg has clarified some of the puzzling aspects of the pathogenesis of this disease Vitamin B_{1} is also active orally if given in very large

amounts (60 to 100 μg) but its hematopoietic effectiveness is greatly increased by normal human gastric juice Vitamin B_1 is apparently the extrinsic factor as well as the liver factor or anti pernicious anemia principle The role of the gastric or intrinsic factor is simply to promote the absorption of vitamin B_1 from the alimentary tract possibly through an action on the intestinal wall rather than on vitamin B_1 itself Because of the absence of intrinsic factor in cases of pernicious anemia the absorption of vitamin B_1 is impaired and the effects of deficiency ultimately develop

The vitamin pteroylglutamic acid (folic acid) has been shown to produce a hematopoietic response in pernicious anemia when given orally or parenterally It is neither Castle s intrinsic factor nor the extrinsic factor In nature it is found in conjugated form as the heptaglutamate (yeast) or as triglutamate An observation of great practical importance is that whereas the administration of liver extract or vitamin B_1 prevents the development or advancement of the neural manifestations of pernicious anemia these may appear in spite of folic acid therapy

It seems likely that vitamin B_1 and folic acid act as coenzymes at different stages in the biologic synthesis of nucleoproteins and that a deficiency of either or both results in a number of abnormalities of which megaloblastic bone marrow is the most readily recognized In explanation of the progress of the neural changes observed in some patients with pernicious anemia receiving folic acid therapy it has been suggested that folic acid influences only desoxyribonucleic acid (DNA) synthesis whereas vitamin B_1 is necessary for the production of ribonucleic acid (RNA) as well as DNA If the latter is required particularly by the bone marrow it is possible that the administration of folic acid while correcting hematologic manifestations tends to exhaust the limited supply of materials needed for RNA synthesis the latter being important for the nervous system

The red corpuscles of patients with untreated pernicious anemia appear to have a shortened survival time Thus the bilirubinemia and urobilinogenuria so characteristic of pernicious anemia would seem to be manifestations of a more rapid blood destruction which may be the consequence of imperfect construction of the red corpuscles resulting from a deficiency of building materials That this is not the sole explanation of the disturbance in pigment metabolism in pernicious anemia however is suggested by the observation that 40 per cent or more of labeled stool urobilin in pernicious anemia is not derived from circulating red corpuscles Some of the pigment apparently comes from heme or hematin which has not been used for hemoglobin synthesis

Pathology The significant findings are in the alimentary tract the bone marrow and the nervous system The tongue usually appears smooth and the papillae may be absent Atrophy of the mucous membrane may be striking in the tongue and in the stomach The changes in the stomach have been observed particularly in the fundic zone where the parietal and chief cells are usually absent

Appropriate staining reveals the liver as well as the spleen and kidneys to be abnormally laden with iron In the liver this is found in the periphery of the lobules and in the Kupffer cells There may also be fatty degeneration in the central cells of the lobules of the liver The heavy deposit of iron is the consequence of the fault in red corpuscle formation which leads to the development of anemia when active blood regeneration follows liver therapy the iron is used in blood formation

The *bone marrow* is red and is found to be crowded with cells Cells of the red series make up 30 to 50 per cent rather than about 20 per cent of the cells of the marrow The degree of hyperplasia and the degree of immaturity of the cells are roughly proportional to the severity of the anemia The nucleated red corpuscles (megaloblasts) differ from those found in other types of anemia in several respects They are exceptionally large and what is more significant the nuclear chromatin is fine and sievelike unlike the relatively coarse and lumpy material seen in normoblasts The cytoplasm of these cells may be polychromatophilic or orthochromatic and in a few is basophilic Many abnormal mitotic figures may be present At the same time extraordinarily large leukocytes may be found in the marrow in particular large metamyelocytes can be seen with bizarre shaped nuclei and peculiarly staining or vacuolated cytoplasm Megakaryocytes may be reduced in number and may be morphologically abnormal In spite of the evidence of cellular activity hematopoiesis is inefficient and anemia develops

In the nervous system degenerative changes may be found in the dorsal and lateral tracts of the cord in the dorsal root ganglions and in the peripheral nerves Myelin degeneration and loss of nerve fibers occur *More rarely changes are encountered in the* brain

Symptomatology The onset of the disease is generally insidious In many instances at least two of the diagnostic triad of symptoms are encountered namely weakness sore tongue and numbness and tingling in the extremities However other complaints may overshadow these and the presenting clinical picture may suggest some disorder of the digestive tract because of anorexia diarrhea and various other gastrointestinal symptoms it may simulate cardiac dysfunction of the anginal or the congestive failure type or one may be led to search

for some malignant neoplasm or an obscure infection In some instances the neural involvement is *so pronounced that a primary neurologic disease* is considered Even renal or genitourinary disease or a mental disorder may be simulated

The degree of soreness of the tongue varies *greatly and the involvement may be complete or* patchy The tongue may be beefy red when the symptoms are pronounced and is less red and smooth when they subside The gastrointestinal *symptoms are very variable However* one consistently found in relapse is anorexia Symptoms referable to the circulatory system include dyspnea palpitation sensations of extra beats weakness *vertigo tinnitus and precordial pain* Since pernicious anemia often appears for the first time in the older age groups it may be difficult to determine to what extent anemia or the degenerative changes of old age have contributed to the development of heart failure

Pallor a flabby rather than wasted appearance a slight or pronounced *yellowish color of the skin* together with faint icterus of the scleras a tongue which is often glazed in appearance and sometimes is red and sore a rapid pulse with slight cardiac *enlargement and often precordial hemic murmurs* in many a spleen which is just palpable and often a slightly enlarged liver are the chief findings outside the nervous system In the nervous system *loss of vibratory sense in the lower extremities (not* necessarily symmetric) incoordination of the lower extremities loss of finer coordination of the fingers signs suggestive of lateral as well as posterior spinal *cord involvement and evidence of peripheral nerve* degeneration are the most common findings and may be present in all degrees from slight or none to extensive involvement Positive Babinski response positive Romberg's sign disturbed position sense spasticity increased or diminished reflexes and sphincter disturbances may be encountered *Minor mental disturbances* (irritability memory disturbances mild depression) or more serious mental symptoms may develop

Laboratory Findings *Blood* The anemia is usually *more severe than the complaints and physical* examination would lead one to suspect In the blood smear macrocytes often oval in shape are characteristically seen (Fig 156) but there is actually a great range in the size of the cells and in addition many bizarre shaped corpuscles are found (poikilocytosis) Since the abnormally large cells *predominate the mean corpuscular volume* is found to be greater than normal and ranges between 100 and 160 μ (Fig 157) There is a corresponding increase in the hemoglobin content of the red corpuscles (mean corpuscular hemoglobin) so that the concentration of hemoglobin in the corpuscles (mean corpuscular hemoglobin concen

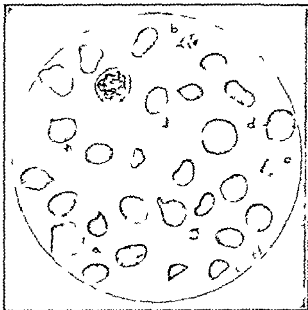


FIG 156 Drawing of a blood smear from a case of pernicious anemia in relapse From a preparation stained with Wright's and magnified ×960 Note the extreme variation in the size and shape of the red corpuscles the large polychromatophilic red corpuscle (*a*) the cells *containing nuclear remnants* and Howell Jolly bodies (*b c*) and a Cabot ring (*c*) the granular red corpuscle (*d*) and the multisegmented polymorphonuclear leukocyte (*Wintrobe Clinical Hematology" Philadelphia Lea & Febiger*)

tration) is normal The red corpuscles in pernicious anemia and in other macrocytic anemias are not "hyperchromic but being thicker as well as larger in diameter than normal corpuscles they appear to be supersaturated with hemoglobin as one looks *at them through a microscope Some degree of* diffuse polychromatophilia as well as basophilic stippling is found and occasional nucleated red corpuscles may be encountered The most striking changes described in classic cases are observed only when the anemia is very severe Since the anemia is macrocytic the red corpuscle count is *reduced more than proportionately as compared* with the hemoglobin or the volume of packed red corpuscles Reticulocytes are usually within normal limits in untreated patients or at most do not run higher than 3 or 4 per cent

The leukocyte count is usually lower than normal chiefly because of a granulocytopenia Thus there *is relative lymphocytosis* The polymorphonuclear neutrophilic leukocytes often show an unusual number of segments and may be exceptionally large An occasional myelocyte is present in many cases Sometimes *some degree of eosinophilia is* encountered The platelets are generally reduced in number sometimes to levels below 100 000 per cubic

amounts (60 to 100 μg) but its hematopoietic effectiveness is greatly increased by normal human gastric juice Vitamin B_{12} is apparently the extrinsic factor as well as the liver factor or anti pernicious anemia principle The role of the gastric or intrinsic factor is simply to promote the absorption of vitamin B_{12} from the alimentary tract possibly through an action on the intestinal wall rather than on vitamin B_{12} itself Because of the absence of intrinsic factor in cases of pernicious anemia the absorption of vitamin B_{12} is impaired and the effects of deficiency ultimately develop

The vitamin pteroylglutamic acid (folic acid) has been shown to produce a hematopoietic response in pernicious anemia when given orally or parenterally It is neither Castle's intrinsic factor nor the extrinsic factor In nature it is found in conjugated form as the heptaglutamate (yeast) or as triglutamate An observation of great practical importance is that whereas the administration of liver extract or vitamin B_{12} prevents the development or advancement of the neural manifestations of pernicious anemia these may appear in spite of folic acid therapy

It seems likely that vitamin B_{12} and folic acid act as coenzymes at different stages in the biologic synthesis of nucleoproteins and that a deficiency of either or both results in a number of abnormalities of which megaloblastic bone marrow is the most readily recognized In explanation of the progress of the neural changes observed in some patients with pernicious anemia receiving folic acid therapy it has been suggested that folic acid influences only desoxyribonucleic acid (DNA) synthesis whereas vitamin B_{12} is necessary for the production of ribonucleic acid (RNA) as well as DNA If the latter is required particularly by the bone marrow it is possible that the administration of folic acid while correcting hematologic manifestations tends to exhaust the limited supply of materials needed for RNA synthesis the latter being important for the nervous system

The red corpuscles of patients with untreated pernicious anemia appear to have a shortened survival time Thus the bilirubinemia and urobilinogenuria so characteristic of pernicious anemia would seem to be manifestations of a more rapid blood destruction which may be the consequence of imperfect construction of the red corpuscles resulting from a deficiency of building materials That this is not the sole explanation of the disturbance in pigment metabolism in pernicious anemia however is suggested by the observation that 40 per cent or more of labeled stool urobilin in pernicious anemia is not derived from circulating red corpuscles Some of the pigment apparently comes from heme or hematin which has not been used for hemoglobin synthesis

Pathology The significant findings are in the alimentary tract the bone marrow and the nervous system The tongue usually appears smooth and the papillae may be absent Atrophy of the mucous membrane may be striking in the tongue and in the stomach The changes in the stomach have been observed particularly in the fundic zone where the parietal and chief cells are usually absent

Appropriate staining reveals the liver as well as the spleen and kidneys to be abnormally laden with iron In the liver this is found in the periphery of the lobules and in the Kupffer cells There may also be fatty degeneration in the central cells of the lobules of the liver The heavy deposit of iron is the consequence of the fault in red corpuscle formation which leads to the development of anemia when active blood regeneration follows liver therapy the iron is used in blood formation

The *bone marrow* is red and is found to be crowded with cells Cells of the red series make up 30 to 50 per cent rather than about 20 per cent of the cells of the marrow The degree of hyperplasia and the degree of immaturity of the cells are roughly proportional to the severity of the anemia The nucleated red corpuscles ("megaloblasts") differ from those found in other types of anemia in several respects They are exceptionally large and what is more significant the nuclear chromatin is fine and sievelike unlike the relatively coarse and "lumpy" material seen in normoblasts The cytoplasm of these cells may be polychromatophilic or orthochromatic and in a few is basophilic Many abnormal mitotic figures may be present At the same time extraordinarily large leukocytes may be found in the marrow in particular large metamyelocytes can be seen with bizarre shaped nuclei and peculiarly staining or vacuolated cytoplasm Megakaryocytes may be reduced in number and may be morphologically abnormal In spite of the evidence of cellular activity hematopoiesis is inefficient and anemia develops

In the nervous system degenerative changes may be found in the dorsal and lateral tracts of the cord in the dorsal root ganglions and in the peripheral nerves Myelin degeneration and loss of nerve fibers occur More rarely changes are encountered in the brain

Symptomatology The onset of the disease is generally insidious In many instances at least two of the diagnostic triad of symptoms are encountered namely weakness sore tongue and numbness and tingling in the extremities However other complaints may overshadow these and the presenting clinical picture may suggest some disorder of the digestive tract because of anorexia diarrhea and various other gastrointestinal symptoms it may simulate cardiac dysfunction of the anginal or the congestive failure type or one may be led to search

for 7 to 10 days until a positive or negative result has been obtained

The discovery of vitamin B_1 and the fact that the cobalt contained therein can be labeled radioactively have provided a method whereby the absorption of this vitamin can be measured. This provides a means by which defective absorption of the vitamin from the gastrointestinal tract can be demonstrated even in the absence of anemia as in treated cases of pernicious anemia and to some extent megaloblastic macrocytic anemias other than pernicious anemia can be differentiated from that condition. Several different techniques are available but the most commonly used one the *Schilling test* depends on measurement of the excretion of the administered radioactive material in the urine. When radioactive vitamin B_1 is given by mouth to persons who can absorb it radioactivity will appear in the urine if the person is flooded with an intramuscular injection of nonradioactive vitamin B_1. Normal individuals have been found to excrete 7 to 22 per cent of the orally administered radioactivity in the urine in 24 hr with an average of 14 2 per cent. Patients with pernicious anemia have been observed to excrete only 0 to 2 3 per cent under these conditions. In them the simultaneous administration of intrinsic factor and radioactive vitamin results in increased excretion up to 3 1 to 30 per cent

Prognosis. With appropriate therapy it is now possible to restore the blood to normal and to promote a return of the general nutrition to normal. If changes are present in the nervous system their advance can at least be halted and in some cases improvement may take place. The danger in pernicious anemia arises from failure to continue therapy and from complications and intercurrent conditions. In a chronic ailment like pernicious anemia other diseases develop in the course of time. Among these carcinoma of the stomach is particularly noteworthy since the incidence of this disease in patients with pernicious anemia is more than three times as great as in other individuals. When changes in the nervous system exist particularly if they involve the urinary sphincter infection may occur. The existence of infection at the time of relapse may seriously interfere with the response to therapy

Treatment Treatment in so far as the blood changes are concerned is extremely simple. The administration of an adequate amount of liver extract or vitamin B_1 is followed by a reticulocyte response which reaches its maximum 5 to 7 or 8 days following initiation of therapy. This is succeeded as the reticulocyte count falls to normal by a rapid disappearance of anemia and by the production of cells of normal size and shape. The leukocyte and the platelet counts likewise return to normal bilirubinemia disappears and the increased quantities of urobilinogen in the urine and stools are reduced to the normal range. The gastric achlorhydria persists

Effective treatment may produce subjective improvement within 48 hr and evidence of a change is often noted by the patient before the reticulocytes increase. There is a gain in appetite and a sense of well being. Tongue symptoms if present disappear promptly. On the other hand neural symptoms do not change quickly. Although in the course of 2 months from the beginning of treatment the patient usually attains a normal blood the neurologic symptoms may still be present however those of milder intensity may have decreased or disappeared

The most efficient means of treatment is by the intramuscular injection of vitamin B_1. The effects of the administration of vitamin B_1 in pernicious anemia appear to be in every way similar to those produced by liver extract and like the latter are very much more pronounced when the vitamin is given parenterally than when it is taken orally (60 to 100 times). The minimal effective intramuscular dose of vitamin B_1 is 1 μg and good hematopoietic responses may be expected from doses of 10 μg daily. Larger amounts up to 80 μg or more daily produce greater effects the mean response being roughly proportional to the logarithm of the dose. As larger doses are given however a greater proportion is promptly excreted

For a patient in relapse between 1 000 and 5 000 μg vitamin B_1 is given since the substance is needed not only to produce a remission but to replenish the greatly depleted body stores. However this is best administered in divided doses in the course of the first 2 weeks or more of therapy otherwise much of the vitamin will be excreted before it can be used or stored as already indicated. An injection of 100 μg is a satisfactory amount to be given at one time. If possible reticulocytes should be counted daily in order that the effectiveness of therapy may be demonstrated early. An increased quantity of red cells as measured by the volume of packed red cells is not usually detectable before 10 days

Maintenance therapy may be calculated on the basis of approximately 2 μg vitamin B_1 for each day but this does not need to be given at intervals shorter than a month or two i e 60 μg is injected intramuscularly every 30 days or 120 μg every 60 days

Intravenous therapy is unnecessary. Oral therapy with liver extract or B_1 –intrinsic factor combinations is inconvenient since daily intake is necessary. Only where some idiosyncrasy on the part of the patient exists or where sensitivity to the parenteral administration of vitamin B_1 cannot be overcome otherwise is oral therapy justified. The substances available are dry or liquid liver extract powdered

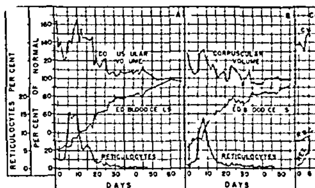


FIG 157 Variations in mean volume of red corpuscles compared with reticulocyte count in three cases of pernicious anemia The mean corpuscular volume (CV) and the red cell count (RBC) are represented as percentages of their respective average normal values By this method the red cell count and mean corpuscular volume of a hypothetic normal individual would fall on the line at 100 per cent Reticulocytes are recorded directly The abscissa records days following the commencement of liver therapy (Wintrobe *Relation of Variations in Mean Corpuscular Volume to Number of Reticulocytes in Pernicious Anemia J Clin Invest* 13 669 1934)

millimeter and bizarre forms including giant platelets may be found When there is thrombocytopenia the bleeding time may be prolonged the blood clot retracts poorly and purpura may develop

The resistance of the red corpuscles to hypotonic saline solutions is not significantly altered The icterus index usually ranges between 8 and 15 sometimes it is as high as 20 or 25 The average plasma bilirubin content is 1 mg per 100 ml but sometimes is higher and the van den Bergh reaction is "indirect"

Other Laboratory Findings With extremely rare exceptions there is in cases of pernicious anemia persistent failure to secrete hydrochloric acid in the stomach even following the injection of histamine Furthermore in the great majority of cases the enzymes are deficient as well and only a small amount of mucus rewards the gastric extraction

In addition to the bilirubinemia already mentioned the urobilinogen content of the urine and stools is increased Detailed examinations reveal many other evidences of metabolic disturbance involving especially protein and uric acid as well as fat metabolism

Diagnosis When the combination of the classic symptoms weakness sore tongue and numbness and tingling together with macrocytic anemia and achlorhydria is found there need be no difficulty in diagnosis Confusion may arise if the symptoms have led one to suspect some other condition and the blood examination has not been appropriate to demonstrate the existence of a macrocytic anemia Confusion may also arise when symptoms referable to the nervous system are prominent and anemia is only moderate or slight in degree For all practical purposes since achlorhydria is so characteristic a feature of pernicious anemia a diagnosis of pernicious anemia should never be made without demonstrating a failure to secrete hydrochloric acid following the injection of histamine The existence of a macrocytic anemia as indicated by calculation of red corpuscle size should furthermore be confirmed by examination of the blood smear In practically all cases such anemia is found to be associated with evidences of altered pigment metabolism such as some increase in plasma bilirubin and an increased output of urobilinogen in the urine and stools Where anemia is slight in degree the combination of achlorhydria slight macrocytosis as indicated by calculation of mean corpuscular volume and by the presence of macrocytes in the blood smear together with a slight degree of bilirubinemia makes the case highly likely

It must be kept in mind that the demonstration of macrocytic anemia is not in itself diagnostic of pernicious anemia for as already indicated macrocytic anemia may appear under a variety of circumstances When the macrocytic anemia is part of another disorder such as "aplastic" anemia "aleukemic" leukemia or some type of hemolytic anemia differentiation is important for vitamin B_1 or folic acid therapy is then valueless In aplastic anemia achlorhydria is only sometimes present glossitis is rare and signs of involvement of the nervous system such as loss of vibratory sense are unusual In aleukemic leukemia, sternal marrow examination should reveal a characteristic picture quite different from that of pernicious anemia and in hemolytic anemia the marrow is normoblastic not megaloblastic Even when the macrocytic anemia is accompanied by megaloblastic bone marrow differentiation is important since some forms unlike pernicious anemia are not permanent in character and do not require treatment for the remainder of the patient's life Certain rare megaloblastic macrocytic anemias furthermore do not respond to the administration of refined liver extract or to vitamin B_1 Some of these conditions are described briefly below

It is important that diagnosis be established accurately before treatment is initiated since as already indicated a diagnosis of pernicious anemia implies the need for therapy for the rest of the patient's life In doubtful cases a *therapeutic test* if properly performed can be very helpful It is important however that the test be made with vitamin B_1 alone and not with some agent containing iron or other substances in addition and that the reticulocyte response be observed daily

genesis of the macrocytic anemia seen in association with *intestinal strictures* and *anastomoses* has been attributed to impaired absorption but the fact that good hematopoietic responses have been observed when Aureomycin or Terramycin was given makes plausible the thesis that the anemia is caused by the colonization of the small intestine by abnormal bacteria which in some way divert folic acid or vitamin B_{12} from the host

The available evidence suggests that vitamin B_{12} and folic acid act as coenzymes at different stages in the biologic synthesis of nucleoproteins (p 1176) and that a deficiency of either or both results in a number of abnormalities of which megaloblastic bone marrow is the most readily recognized Under certain circumstances dietary deficiency of folic acid may develop and result in nutritional macrocytic anemia In other patients there may be defective absorption of folic acid (sprue idiopathic steatorrhea) but in some such patients the absorption of vitamin B_{12} may be impaired as well In still other cases alterations in the gastrointestinal tract may lead to consumption or destruction of one or both of these substances or an antimetabolite may be produced there (fish tapeworm anemia intestinal strictures and anastomoses) Only following total gastrectomy is absorption of vitamin B_{12} impaired in a manner corresponding to that encountered in pernicious anemia i e as the result of lack of intrinsic factor Various combinations of defects in dietary content absorption consumption destruction or antagonism may result in various degrees of deficiency of vitamin B_{12} or folic acid or both In addition it has been postulated that vitamin B_{12} in some manner influences the storage absorption and utilization of folic acid and that when vitamin B_{12} is lacking these functions are impaired

Quite unexplained are the more than a dozen instances of megaloblastic macrocytic anemia which have been observed in patients undergoing anticonvulsant therapy with either diphenylhydantoin sodium or Promidone Prohibition of the anticonvulsant particularly when associated with administration of folic acid resulted in complete relief of the anemia

Although macrocytic anemia is seen in some cases of hypothyroidism it is noteworthy that the bone marrow is hypoplastic and normoblastic and desiccated thyroid not liver extract vitamin B_{12} or pteroylglutamic acid is effective in relieving the anemia Likewise the macrocytic anemia encountered in association with some cases of severe chronic liver disease should not be classed with the megaloblastic macrocytic anemias since the bone marrow is usually normoblastic and a response to liver extract therapy or vitamin B_{12} has been seen only in rare cases //- y

HEMOLYTIC ANEMIAS

Manifestations Under the heading of hemolytic anemias a number of conditions can be included which differ widely in etiology symptomatology severity and course The symptoms depend upon the rapidity and extent of hemolysis its duration and whether or not hemolysis is taking place in the blood stream or in the reticuloendothelial system Jaundice is a sign common to all but its degree may be such as to be barely perceptible (when it is often overlooked) or so great as to be very striking Other symptoms may be entirely absent Thus patients with hereditary spherocytosis are more yellow than sick except when a hemolytic crisis occurs In other cases there may be slowly progressive anemia and gradually increasing jaundice The anemia may become profound and yet there may be few manifestations since in such cases there is time for cardiovascular adjustments (p 202) to be made In chronic hemolytic anemia splenomegaly is common and enlargement of the liver may be present Complications such as gall bladder disease or chronic leg ulcers may develop

On the other hand the onset of hemolytic anemia may be heralded by a severe shaking chill followed by high fever malaise headache and pain in the back abdomen or limbs The abdominal pain may be so severe and may be accompanied by such marked muscular rigidity and spasm as to simulate an acute surgical condition If the hemolysis is rapid and severe enough profound prostration and shock accompanied by anuria and oliguria may ensue When urine is passed it is found to be very dark Jaundice develops rapidly As anemia ensues weakness palpitation dyspnea tachycardia cyanosis cardiac enlargement hemic murmurs vertigo faintness and other manifestations of rapidly developing anemia (Chap 22) make their appearance In certain types of acute hemolytic reactions urticaria vascular disturbances suggesting Raynaud s phenomenon and thrombosis and gangrene may develop

All grades from such acute fulminating disorders of several days duration to extremely benign conditions of many years standing may be encountered A chronic congenital process may be interrupted by acute exacerbations

Hematologic Manifestations The hematologic manifestations which accompany acute blood destruction consist of an initial phase of rapid destruction of red corpuscles and a second phase of rapid blood regeneration These two phases usually overlap especially when the hemolytic agent acts over a prolonged period of time

The anemia may be mild or severe depending upon the intensity and duration of the hemolytic process It is usually normocytic but may be macro

stomach or liver with stomach (USP XIV) and vitamin B_1 –intrinsic factor combinations These should be given in doses of 1 USP unit per day Pteroylglutamic acid (folic acid) 5 to 20 mg daily has also been used in such cases but since it may fail to protect the patient against the development of changes in the nervous system this procedure is not recommended

The diet should be such as to restore the patient to a state of normal nutrition and to maintain him so but need not contain any unusual foods except perhaps where neurologic changes are present In such cases it may be wise to recommend the consumption of say a half pound or more of cooked liver per week This recommendation is made since information is still lacking as to the exact nature of the deficiency which leads to the development of changes in the nervous system By the consumption of whole liver the patient possibly obtains substances of value in addition to the antianemic factor

Transfusion is rarely if ever required in per*nicious anemia since a physiologic response can* be achieved in 48 to 72 hr if vitamin B_1 is given parenterally Since the patient s anemia has developed gradually he has become adjusted to the existent anemia Where the cardiovascular system seems imperfect transfusion by producing a sudden increase in blood volume may sometimes be harmful and may precipitate acute cardiac failure with pulmonary edema Iron is not needed as an adjunct except where iron deficiency exis s as well Supplementary therapy with various vitamins is likewise unnecessary These can be and should be furnished in the diet in the form of food The administration of dilute hydrochloric acid (USP) in amounts of 4 to 8 ml t i d with meals is sometimes of value when gastrointestinal complaints persist particularly eructations or frequent bowel movements In the absence of such complaints hydrochloric acid is unnecessary

Particularly where changes in the nervous system exist confinement to bed should be as brief as possible and the patient should be encouraged to use the limbs even when lying in bed In addition passive movement massage and dry heat are valuable for improving the tone of the muscles Physiotherapy may permit adjustment to permanent damage resulting from the neurologic changes

The development of an intercurrent disease particularly infection calls for an increase in the amount of liver extract or vitamin B_1 therapy since requirements under such conditions seem to be increased

Vitamin B_1 therapy has now essentially replaced treatment with liver extract Even when refined liver extracts were used sensitivity was sometimes observed to develop in the form of severe flushing dizziness a sense of oppression or urticaria following its intramuscular administration Sometimes even peripheral vascular collapse occurred Sensitivity to the crystalline vitamin B_1 is extremely rare

Megaloblastic Macrocytic Anemias Other than Pernicious Anemia

Nutritional Macrocytic Anemia This term refers to macrocytic anemia arising from dietary deficiency as distinguished from deficiency resulting from lack of intrinsic factor or from faulty absorption Since such anemia has been seen most often in the tropics *tropical macrocytic anemia* is another synonym The condition is particularly common in pregnant women Weakness shortness of breath sore mouth sore tongue diarrhea and edema are common complaints In contrast to pernicious anemia in nutritional macrocytic anemia achlorhydria is no more common than in the popu*lation in general and degenerative changes in the* nervous system are practically never found The blood picture and bone marrow are indistinguishable from those of pernicious anemia Tropical macrocytic anemia probably is not a single clinical entity In many cases the anemia has been relieved by the administration of yeast Marmite (autolyzed yeast) or liver In some cases a good hematopoietic response has followed the administration of pteroylglutamic acid and in a few a good response to vitamin B_1 and even to oral penicillin has been reported In certain cases however these agents have not been effective and the need for still an other factor (Wills s factor) has been postulated That some form of dietary deficiency is the cause of this disorder is indicated by the observation that it does not recur if the diet is satisfactory

Nutritional macrocytic anemia is uncommon in the Temperate Zones Few of the instances of macrocytic anemia seen in *pellagra* can be accounted for by a lack of extrinsic factor in the diet In other cases faulty absorption is important and in many both mechanisms play a role In *sprue* and in *idiopathic steatorrhea* as described elsewhere (p 528) inadequate absorption is the main cause for the development of macrocytic anemia In Great Britain in particular *occult idiopathic steatorrhea with* insignificant alimentary symptoms but accompanied by megaloblastic macrocytic anemia is not uncommon This usually responds much better to the administration of pteroylglutamic acid than to vitamin B_1

Macrocytic anemia that occurs following *total gastrectomy* is the consequence of lack of intrinsic factor The absorption of orally administered vitamin B_1 has been shown to be impaired The patho

genesis of the macrocytic anemia seen in association with *intestinal structures* and *anastomoses* has been attributed to impaired absorption but the fact that good hematopoietic responses have been observed when Aureomycin or Terramycin was given makes plausible the thesis that the anemia is caused by the colonization of the small intestine by abnormal bacteria which in some way divert folic acid or vitamin B_{12} from the host

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On the other hand the onset of hemolytic anemia may be heralded by a severe shaking chill followed by high fever malaise headache and pain in the back abdomen or limbs The abdominal pain may be so severe and may be accompanied by such marked muscular rigidity and spasm as to simulate an acute surgical condition If the hemolysis is rapid and severe enough profound prostration and shock accompanied by anuria and oliguria may ensue When urine is passed it is found to be very dark Jaundice develops rapidly As anemia ensues weakness palpitation dyspnea tachycardia cyanosis cardiac enlargement hemic murmurs vertigo faintness and other manifestations of rapidly developing anemia (Chap 22) make their appearance In certain types of acute hemolytic reactions urticaria vascular disturbances suggesting Raynaud s phenomenon and thrombosis and gangrene may develop

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Hematologic Manifestations The hematologic manifestations which accompany acute blood destruction consist of an initial phase of rapid destruction of red corpuscles and a second phase of rapid blood regeneration These two phases usually overlap especially when the hemolytic agent acts over a prolonged period of time

The anemia may be mild or severe depending upon the intensity and duration of the hemolytic process It is usually normocytic but may be macro-

cytic especially during the stage of rapid regeneration when many relatively immature and reticulated cells are present It is not uncommon to find 10 to 25 per cent reticulocytes in chronic cases and as many as 60 per cent or even more in acute cases Polychromatophilia nucleated red blood corpuscles and Howell Jolly bodies are usually present There generally is marked variation in the size of the cells (anisocytosis) and usually little variation in their shape (poikilocytosis) except in patients with sickle cell anemia Spherocytes may be numerous

Marked stimulation of the leukopoietic tissues manifested by leukocytosis and a shift to the left with myelocytes and even rare myeloblasts accompanies the red corpuscle regeneration Platelets may increase in number and large bizarre forms may make their appearance In certain cases however and especially in paroxysmal nocturnal hemoglobinuria leukopenia and thrombocytopenia may be present

The *bone marrow* is hyperplastic There is a great increase in normoblasts and a consequent reduction in the leukocyte/erythrocyte ratio from the normal of 4 or 5 1 to about 1 1 or even less The normoblasts are chiefly polychromatophilic and orthochromatic forms as a rule there are not many pronormoblasts or basophilic normoblasts Megaloblasts so characteristic of pernicious anemia and related macrocytic anemias are not present

Pigment Metabolism When the degree and rate of blood destruction are very great hemoglobin is liberated into the plasma and if the hemoglobin binding capacity of the plasma (haptoglobin p 199) is exceeded free hemoglobin is excreted by the kidneys and hemoglobinuria results However the finding of red urine must not be assumed to be necessarily indicative of hemoglobinuria The color may also be produced by intact red corpuscles porphyrin or myoglobin Microscopic and spectroscopic examination of the urine will reveal the cause of the abnormal color Under certain circumstances hematin (p 199) may be released

More often blood destruction is less rapid In such cases hemoglobinemia and hemoglobinuria are not found and there is only an increase in the icterus index serum bilirubin and urobilinogen excretion in the urine and feces The stools assume a dark color and from 300 to 4 000 mg urobilinogen may be found in a 24 hr stool as compared with the normal of 40 to 280 mg The 24 hr urine may contain 5 to 200 mg urobilinogen (normal 0 to 3 5 mg) The fecal urobilinogen may be increased when the urine urobilinogen and the bilirubin in the blood are not significantly greater than normal

The quantity of bilirubin in the plasma may rise as high as 10 mg per cent The reaction is indirect but some increase in direct or "one minute" bilirubin (bilirubin glucuronide) may also occur The intensity of the bilirubinemia depends not only on the extent of the blood destruction but also on the capacity of the liver to remove the pigment from the blood stream and excrete it in the bile A normally functioning liver is capable of excreting large quantities of bilirubin but as anemia and consequent hypoxemia develop its functional capacity becomes impaired and bilirubin accumulates in the blood stream

Classification

The hemolytic disorders may be classified in various ways none of which is entirely satisfactory A clinical classification based on the severity of the manifestations may be confusing since a chronic process may come to notice only during an acute exacerbation Differentiation of congenital and acquired forms is useful Better still however is classification on the basis of pathogenesis even though understanding of the pathogenesis of the hemolytic anemias is still incomplete

By transfusing corpuscles which differ from those of the recipient with respect to their MN or Rh type or by giving group O corpuscles to recipients belonging to one of the other three major blood groups it has been shown that when normal corpuscles are transfused to patients in whom there is an extracorpuscular cause for hemolysis the donated corpuscles are destroyed as rapidly as the patient s own corpuscles If on the other hand the patient s corpuscles are removed from their abnormal environment and transfused to a normal recipient their survival time is normal Hemolytic anemias which have been shown to be or are thought to be of this type are listed in group I of Table 101 Group II includes disorders in which hemolysis is the result of a defect in the patient s own red corpuscles The patient s corpuscles when given to a normal recipient can be shown to be disposed of more rapidly than those of the recipient while the latter s corpuscles if transfused into the patient maintain a normal life span It may be noted that in the main hemolytic anemias due to intracorpuscular defects are familial and hereditary while those produced by extracorpuscular factors are acquired

Acute Hemolytic Anemias Due to Immune Body Reactions The naturally occurring agglutinins α and β cause hemolysis when incompatible blood is given by transfusion When hemolytic transfusion reactions take place in spite of A B and O blood group compatibility they are attributable in most instances to the development of anti Rh (D) agglutinins Next in frequency are the Kell antigen and antibody Other blood groups are only rarely involved (p 418) Such agglutinins are also responsible for the development of hemolytic disease of the newborn (*erythroblastosis fetalis*) a condi

tion in which the red corpuscles of an Rh positive fetus are destroyed as the result of the action of antibodies produced in the Rh negative woman carrying the fetus

Although the number of possible causes of hemolytic anemia is large as Table 101 indicates in a very significant number of cases of acquired hemolytic anemia no cause is found and no associated disease is recognized *Idiopathic cases* have been observed at all ages from five months to seventy eight years but females are more often affected than males The clinical manifestations range in the extremes The course may be acute severe and fulminating or the illness may be insidious in onset and chronic in course In the latter instances repeated attacks of greatly exaggerated blood destruction may punctuate the course and may be followed by spontaneous remissions By and large the manifestations are rarely as mild as they may be in hereditary spherocytosis The hematologic features are similar to those of other hemolytic anemias varying according to the severity of the condition In most instances however certain immunologic manifestations may be demonstrated if they are looked for The introduction of serologic methods like the Coombs test has made possible the demonstration of antibodies in the majority of cases of idiopathic acquired hemolytic anemia

There appear to be several varieties of idiopathic acquired hemolytic anemia They are in part associated with differences in the type of antibody which is found In the majority a "warm" antibody is present i e the antibody reacts well at 37 C and is not potentiated at lower temperatures The most common warm antibodies are incomplete that is they sensitize normal erythrocytes to antiglobulin serum but do not cause agglutination in a saline medium The sensitization is not inhibited by previous heat inactivation of the patient s serum at 56 C and it is increased only slightly by acidification of the serum to pH 6 5 or 7 Typically these warm antibodies cause agglutination and not hemolysis The sensitizing antibodies usually are γ globulins

"Cold" antibodies are markedly potentiated by reducing the temperature below 37 C These antibodies are "incomplete" antibodies but they may also act as "complete" agglutinating antibodies and under certain circumstances may also bring about hemolysis Two main forms of cold antibodies have been demonstrated in acquired hemolytic anemias The common typical type is a powerful antigen the rare variety is similar to the Donath Landsteiner antibody of paroxysmal cold hemoglobinuria In cases of acquired hemolytic anemia associated with the presence of cold antibodies cyanosis and Raynaud s phenomenon on exposure to cold as well as hemoglobinuria may be noted Spherocytes are

Table 101 CLASSIFICATION OF HEMOLYTIC DISORDERS

- I Extracorpuscular causes
  - A Acute hemolytic anemias due to immune body reaction
    - 1 Isoagglutinins anti A anti B (transfusion reactions)
    - 2 Isoagglutinins anti Rh anti Hr Kell Duffy etc (hemolytic disease of the newborn intra group transfusion reactions)
    - 3 Cold hemolysins (paroxysmal cold hemoglobinuria)
  - *B* Idiopathic acquired hemolytic anemias
  - *C* Secondary or symptomatic hemolytic anemias
    - 1 Hodgkin s disease
    - 2 Chronic lymphocytic leukemia lymphosarcoma
    - 3 Disseminated lupus erythematosus
    - 4 Metastatic carcinomatosis
    - 5 Dermoid cysts
    - 6 Liver disease
    - 7 Thrombotic thrombocytopenic purpura
  - *D* Infectious agents
    - 1 Malaria
    - 2 *Bartonella* (Oroya fever)
    - 3 Septicemia *Clostridium welchii Vibrio comma* (cholera) rarely others
    - 4 Viruses (atypical pneumonia infectious mononucleosis)
  - *E* Chemical agents
    - 1 Related to size of dose
      - *a* Phenylhydrazine
      - *b* Naphthalene
      - *c* Trinitrotoluene
      - *d* Benzene
      - *e* Acetanilid
      - *f* Phenacetin
      - *g* Aniline
      - *h* Methyl chloride
      - *i* Arsine
      - *j* Lead
    - 2 Depending on hypersensitivity
      - *a* Sulfonamides
      - *b* Quinine
      - *c* Pamaquine
      - *d* Primaquine
      - *e* p-Aminosalicylic acid
      - *f* Benzedrine
      - *g* Mesantoin
      - *h* Paraphenylenediamine
  - *F* Physical agents (heat—severe thermal burns)
  - *G* Vegetable and animal poisons
    - 1 Vegetable poisons
      - *a* Fava bean (*Vicia faba*)
      - *b* Castor bean (ricin)
    - 2 Animal poisons
      - *a* Snake venoms
- II Intracorpuscular defects
  - A Hereditary spherocytosis (familial or congenital hemolytic jaundice)
  - *B* Hereditary elliptocytosis
  - *C* Hereditary nonspherocytic hemolytic anemias
  - *D* Hereditary leptocytosis (thalassemia Mediterranean anemia)
  - *E* Sickle cell disease
  - *F* Other hereditary hemoglobinopathies (C D E G H I J K)
  - *G* Combinations of thalassemia and sickle-cell disease or other hemoglobinopathies
  - *H* Paroxysmal nocturnal hemoglobinuria

cytic especially during the stage of rapid regeneration when many relatively immature and reticulated cells are present It is not uncommon to find 10 to 25 per cent reticulocytes in chronic cases and as many as 60 per cent or even more in acute cases Polychromatophilia nucleated red blood corpuscles and Howell Jolly bodies are usually present There *generally is marked variation in the size of the cells* (anisocytosis) and usually little variation in their shape (poikilocytosis) except in patients with sickle cell anemia Spherocytes may be numerous

Marked stimulation of the leukopoietic tissues manifested by leukocytosis and a "shift to the left" with myelocytes and even rare myeloblasts accompanies the red corpuscle regeneration Platelets may increase in number and large bizarre forms may make their appearance In certain cases however and especially in paroxysmal nocturnal hemoglobinuria leukopenia and thrombocytopenia may be present

The *bone marrow* is hyperplastic There is a great increase in normoblasts and a consequent reduction in the leukocyte/erythrocyte ratio from the normal of 4 or 5 1 to about 1 1 or even less The normoblasts are chiefly polychromatophilic and orthochromatic forms as a rule there are not many pronormoblasts or basophilic normoblasts Megaloblasts so characteristic of pernicious anemia and related macrocytic anemias are not present

Pigment Metabolism When the degree and rate of blood destruction are very great hemoglobin is liberated into the plasma and if the hemoglobin binding capacity of the plasma (haptoglobin p 199) is exceeded free hemoglobin is excreted by the kidneys and hemoglobinuria results However the finding of red urine must not be assumed to be *necessarily indicative of hemoglobinuria* The color may also be produced by intact red corpuscles porphyrin or myoglobin Microscopic and spectroscopic examination of the urine will reveal the cause of the abnormal color Under certain circumstances hematin (p 199) may be released

More often blood destruction is less rapid In such cases hemoglobinemia and hemoglobinuria are not found and there is only an increase in the icterus index serum bilirubin and urobilinogen excretion in the urine and feces The stools assume a dark color and from 300 to 4 000 mg urobilinogen may *be found in a 24 hr stool as compared with* the normal of 40 to 280 mg The 24 hr urine may contain 5 to 200 mg urobilinogen (normal 0 to 3 5 mg) The fecal urobilinogen may be increased when the urine urobilinogen and the bilirubin in the blood are not significantly greater than normal

The quantity of bilirubin in the plasma may rise as high as 10 mg per cent The reaction is indirect but some increase in direct or one minute bilirubin (bilirubin glucuronide) may also occur The intensity of the bilirubinemia depends not only on the extent of the blood *destruction but also on the* capacity of the liver to remove the pigment from the blood stream and excrete it in the bile A normally functioning liver is capable of excreting large quantities of bilirubin but as anemia and consequent hypoxemia develop its functional ca*pacity becomes impaired and bilirubin* accumulates in the blood stream

Classification

The hemolytic disorders may be classified in various ways none of which is entirely satisfactory A clinical classification based on the severity of the manifestations may be confusing since a chronic process may come to notice only during an acute exacerbation Differentiation of congenital and acquired forms is useful Better still however is classification on the basis of pathogenesis even though understanding of the pathogenesis of the hemolytic anemias is still incomplete

By transfusing corpuscles which differ from those of the recipient with respect to their MN or Rh type or by giving group O corpuscles to recipients belonging to one of the other three major blood groups it has been shown that when normal corpuscles are transfused to patients in whom there is an extracorpuscular cause for hemolysis the donated corpuscles are destroyed as rapidly as the patient s own corpuscles If on the other hand the patient s corpuscles are removed from their abnormal environment and transfused to a normal recipient their survival time is normal Hemolytic anemias which have been shown to be or are thought to be of this type are listed in group I of Table 101 Group II includes disorders in which hemoly*sis is the result of a defect in the patient s own* red corpuscles The patient s corpuscles when given to a normal recipient can be shown to be disposed of more rapidly than those of the recipient while the latter s corpuscles if transfused into the patient maintain a normal life span It may be noted that *in the main hemolytic anemias* due to intracorpuscular defects are familial and hereditary while those produced by extracorpuscular factors are acquired

Acute Hemolytic Anemias Due to Immune Body Reactions The naturally occurring agglutinins α and *β cause hemolysis* when incompatible blood is given by transfusion When hemolytic transfusion reactions take place in spite of A B and O blood group compatibility they are attributable in most instances to the development of anti Rh (D) agglutinins Next in frequency are the Kell antigen and antibody Other blood groups are only rarely involved (p 418) Such agglutinins are also responsible for the development of hemolytic disease of the newborn (*erythroblastosis fetalis*) a condi

molysins have been described as already mentioned Immune hemolysins are not found free in the serum except in disorders which require special conditions for their maximum operation Thus in paroxysmal cold hemoglobinuria a fall in temperature is required for maximum activity of the hemolytic system while in paroxysmal nocturnal hemoglobinuria a fall in the pH of the blood is necessary In most instances immune hemagglutinins remain attached to the red corpuscle The Coombs or "developing" test serves to demonstrate such factors (p 1186)

The role of mechanical factors is indicated by the fact that the osmotic and mechanical fragilities of the red corpuscles increase when the corpuscles are placed in natural or artificial immune serums in which hemolysins and agglutinins are present Similar changes in fragility have been observed in association with the action of hemolytic agents such as saponin or physical factors such as heat Osmotic lysis usually determined by the familiar hypotonic saline fragility test probably does not operate in vivo except perhaps in the spleen under certain conditions It is a plausible hypothesis that mechanical trauma is the ultimate mechanism whereby cell destruction occurs under normal circumstances and in many varieties of hemolytic anemia It has been shown that nearly spherical cells strongly agglutinated cells and those with weakened cell membranes are abnormally susceptible to mechanical destruction In certain cases of acquired hemolytic anemia increased mechanical fragility has been observed when osmotic fragility was normal It was found that such cells did not survive normally in the circulation of normal individuals The increased mechanical fragility of sickled masses of erythrocytes may explain the increased red corpuscle destruction in sickle-cell anemia

The term *erythrostasis* has been applied to the processes to which red corpuscles are subjected when denied free access to fresh plasma The spleen appears to have the property of selectively removing and concentrating spheroidal cells Erythrostasis may lead to increased osmotic and mechanical fragility of the red corpuscles and thereby favor their destruction It has been suggested that the spleen is of importance in congenital hemolytic jaundice because of the inherently abnormal susceptibility of the red corpuscles to the effects of erythrostasis It has been demonstrated that in a patient with congenital hemolytic jaundice who had received transfusions of identifiable normal corpuscles the spleen removed at operation, had selectively retained the patient s own corpu cles Perfusion experiments have shown that even the spleen from a case of purpura hemorrhagica where no hemolytic process ex1 ted likewise selectively removed transfused red corpuscles from cases of congenital hemolytic jaundice but did not retain normal corpuscles

Sequestration in the spleen and also in the liver plays an important role in acquired hemolytic anemias In sequestering sensitized red corpuscles from the circulation the spleen behaves as a highly proficient passive filter Thus it has been shown that when sensitized red corpuscles are injected in the circulation of normal subjects they are agglutinated by the plasma globulins following which they are sequestered in the spleen and are hemolyzed within a few minutes The speed of the hemolysis is such as to suggest the presence of a preformed lysin leukocytes may be involved in this lytic process However in contrast to the fate of these sensitized corpuscles coated with "incomplete" antibodies in reactions involving "complete" antibodies as when red corpuscles are injected into normal subjects hyperimmunized against them sequestration and destruction occur in the liver to a greater extent than in the spleen

Studies of spontaneous hemolysis of red corpuscles in vitro (autohemolysis) have led to the recognition of a metabolic defect in the red corpuscles of hereditary spherocytosis The continued presence of glucose during incubation of the red corpuscles was observed to retard markedly the potassium loss and the increase in osmotic fragility of the cells It was possible to demonstrate that abnormalities in the dynamics of intracellular carbohydrate metabolism exist Thus using radioactive phosphorus as a tracer it was found that in cells from patients with hereditary spherocytosis there is a smaller flux of P^{32} into adenosinetriphosphate and 2 3 diphosphoglyceric acid than in normal cells and a concurrent increase in the flux into orthophosphate It was shown also that in many instances the metabolic lesion could be reversed with adenosine and glucose Thus some of the deleterious effects of erythrostasis can be explained An adequate rate of supply of energy rich phosphate bonds is necessary for the maintenance of the biconcave shape of the red corpuscle Energy production may be defective as the result of genetically controlled enzyme deficiencies or functional inadequacies Such red corpuscles are less well able to maintain their integrity than normal ones

Study of a Patient with a Hemolytic Disorder

Hemolytic anemia can be recognized by the development of certain symptoms and signs certain changes in the blood and bone marrow and characteristic alterations in pigment metabolism as already outlined The differentiation of the various hemolytic disorders is important since treatment depends on their nature The history alone may suffice to reveal an etiologic agent or may indicate that one is dealing with one of the familial or

not conspicuous and osmotic fragility may be normal The course of these cases is generally chronic and often is relatively mild They most commonly occur in elderly persons

In addition to these warm and cold autoantibodies it is not uncommon to find other manifestations of abnormal protein formation in patients with *acquired hemolytic anemia Thus antibodies against* lipoid antigens may be present and may give rise to false positive Wassermann and Kahn reactions This is especially frequent in disseminated lupus erythematosus Again serum complement may be reduced and hypergammaglobulinemia and cryoglobulins may develop

It was assumed at first that the autoantibodies found in acquired hemolytic anemia were nonspecific that is they reacted with all types of human red cells without relation to any known blood group antigens In some cases however the autoantibodies have been found to be specific and were directed against various Rh antigens and more rarely against other blood groups such as Kell B and O The serology of the acquired hemolytic anemias is complicated however Autoantibodies without apparent specificity have been observed in the same blood as those in which specific antibodies were discovered Furthermore it has been observed that the antibodies of one patient often differ considerably from those of another in temperature requirements specificity chemical nature and in their reactions in vitro A few cases have been described in which the patients serums contained *a potent agglutinin for enzyme treated cells* but this was not associated with a positive direct Coombs test In cases in which cold antibodies have been demonstrated there has not been a clear correlation between their titer and hemolysis or such exposure to cold as might be expected to lead to agglutination and subsequent mechanical destruction of the red corpuscles

Certain features serve to distinguish chronic hemolytic anemia with erythrocyte bound antibody from other types of hemolytic anemia As already indicated warm or cold hemagglutinins are present and the Coombs test (p 1186) is positive Spherocytosis is usually marked when the disease is active and at such times the osmotic fragility of the red corpuscles is irregularly increased and their mechanical fragility is also increased Even normal transfused cells become spherical their fragility becomes increased and they are rapidly destroyed In quiescent stages however the spherocytosis may be absent and osmotic and mechanical fragility may be normal

It has been pointed out that oxalated blood from patients with hemolytic anemia associated with immune bodies may have a granular appearance when examined with a hand lens as the blood is allowed to flow in a thin layer along the side of a glass container In rare cases this may even be seen with the naked eye The phenomenon is attributable to the agglutination of the red corpuscles in the plasma

Other Hemolytic Anemias Presumably Due to Extracorpuscular Causes The clinical manifestations of the hemolytic anemias associated with various disorders (symptomatic hemolytic anemias) are similar to those in cases of the idiopathic variety except for the presence of manifestations of the underlying disease The latter however are sometimes not apparent and must be sought out carefully *Although it was at first thought that erythro*cyte bound antibodies do not develop in cases of symptomatic hemolytic anemia with the introduction of appropriate serologic techniques it is becoming clear that at least a great proportion of these cases are of the immune body type

Table 101 lists the large variety of infectious chemical and physical agents which may be associated with the development of hemolytic anemia Of the chemical agents some such as saponin act directly on the red corpuscles Others depend for their action on an abnormality of the host (sensitivity) It has been shown that there is an intrinsic abnormality in the red corpuscles of persons sensitive to sulfanilamide acetanilid phenacetin naphthalene primaquine phenylhydrazine thiazolsulfone (Promizole) sulfoxone (Diasone) and nitrofurantoin (Furadantin) The abnormality consists in a reduced glutathione content and defective en*zymatic protection against damage by one of these* drugs This appears to be due to reduced glucose 6 phosphate dehydrogenase activity in the sensitive cells There is evidence that the sensitivity to the fava bean which results in the development of hemolytic anemia (*favism*) depends on a similar mechanism The red cell abnormality in these sensitive persons differs from that seen in disorders classified in Table 101 under the general heading of Intracorpuscular Defects such as hereditary spherocytosis in that the red cell abnormality of sensitive persons per se has no known deleterious effect on the individual or on the red cell life span *in the absence of the offending chemical agent*

Intracorpuscular Defects A number of the disorders coming under this head are described separately below

Mechanisms of Hemolysis Various processes condition or cause the destruction of red *corpuscles* phagocytosis agglutinins and hemolysins *osmotic* lysis mechanical factors and sequestration with erythrostasis The importance of phagocytosis is not clear Some regard it as a primary and important factor *while others relegate it to an accessory role dependent on other mechanisms* of red corpuscle destruction Various types of hemagglutinins and he

Table 102 COOMBS TEST

Hemolytic disorder	Antihuman globulin serum mixed with patient's RBCs (*direct*)	Antihuman globulin serum mixed with normal RBCs after incubation in patient's serum (*indirect*)	
		RH+	*RH−*
Acquired hemolytic anemia			
With circulating antibodies	+	+	+
Without circulating antibodies	+	−	−
Due to Rh antibodies in Rh+ infant (erythroblastosis fetalis)	+	+	−
Due to physical or chemical agents	±	−	−
Congenital hemolytic anemia (hereditary spherocytosis)	−	−	−
Sickle-cell anemia	−	−	−
Paroxysmal nocturnal hemoglobinuria	−	−	−
Paroxysmal cold hemoglobinuria (type associated with syphilis)	+	−	−

The occasional finding of a positive Coombs test in this and in other hemolytic anemias where the test is usually negative is explained by superimposed frequently transient episodes of acquired hemolytic anemia

glutinin and the treatment of the red corpuscles with proteolytic enzymes such as papain and trypsin which renders them more susceptible to the demonstration of antibodies For the antibody tests it is necessary in some instances to use the patient's own red corpuscles rather than any available group O red corpuscles as is often the practice

Prognosis and Treatment Prognosis and treatment *depend on the nature and cause of the hemolytic disorder* The causative agent such as a parasite or chemical if discovered must be removed An acute attack of hemolysis requires rest maintenance of fluid balance and relief of pain Blood transfusion may be dangerous if the cause of the hemolysis is extracorpuscular and still operating for then the introduced blood may also be destroyed Yet when blood destruction is so acute that hemoglobinemia and hemoglobinuria are present the possibility of death from circulatory collapse is so great that frequent and sometimes massive blood transfusions must be given

An important advance in the management of many cases of acquired hemolytic anemia is the discovery that the administration of adrenocorticotropic hormone (ACTH) or of prednisone or cortisone will control the hemolytic manifestations The latter are preferable since they can be given orally As much as 60 to 100 mg prednisone or 200 to 400 mg cortisone per 24 hr may be required In some instances transfusion can be withheld entirely while in other cases where the anemia is so severe that transfusion is necessary blood can be given with much less chance of a reaction if cortisone or ACTH therapy has been started As in the treatment of other disorders the usual precautions such as salt restriction and *administration of potassium chloride* should be taken when these agents are used in the treatment of hemolytic anemia

Splenectomy while almost invariably beneficial in hereditary spherocytosis is much less successful in the acquired forms Furthermore if carried out in an acute hemolytic phase the operative mortality is high In idiopathic acquired hemolytic anemia *therefore the hormones should be used first* at least in preparation for operation Unfortunately neither splenectomy nor hormone therapy is permanently helpful in all cases in many the evidence of hemolysis returns when hormone therapy is interrupted

In some cases of "symptomatic hemolytic anemia treatment of the underlying disorder when possible relieves the hemolytic anemia as well When this does not occur a trial of steroid therapy is justified In certain instances splenectomy may be helpful especially if leukopenia and thrombocytopenia are also present and the picture is that of hypersplenism

Splenectomy is of no value in sickle cell anemia thalassemia or paroxysmal nocturnal hemoglobinuria

Paroxysmal Cold Hemoglobinuria

This is an uncommon disorder characterized by the sudden passage of hemoglobin in the urine following local or general *exposure to cold* Aching and pain in the back legs or abdomen and other symptoms of acute hemolysis such as a chill fever and malaise are associated with the passage of dark brownish urine Other findings are those characteristic of acute hemolytic anemia Symptoms may

hereditary disorders Physical examination may reveal one of the conditions of which hemolytic anemia can be symptomatic In addition certain simple tests have been devised which give some clue to the nature of the disorder

Osmotic Fragility Test In certain cases of hemolytic anemia one demonstrates by this test the susceptibility of red corpuscles to hemolysis in concentrations of salt which fail to cause rupture of normal corpuscles Such osmotic fragility is characteristic of corpuscles which are more nearly spherical than normal corpuscles The test is generally positive in hereditary spherocytosis and negative in acquired forms Unfortunately however there are exceptions to this statement Spherocytosis and increased osmotic fragility are encountered in certain acquired cases especially in an acute phase The sensitivity of the test can be increased by first incubating the corpuscles to be tested in vitro at body temperature for 24 hr Under such conditions the fragility of normal corpuscles is increased slightly that of corpuscles from cases of hereditary spherocytosis is increased markedly and symmetrically

Mechanical Fragility Test A small amount of oxalated or defibrinated blood is placed in an Erlenmeyer flask containing glass beads and rotated following which the hemoglobin liberated from the cells is measured and compared with controls Increased mechanical fragility has been observed in congenital hemolytic jaundice in sickle cell anemia and in the presence of cold agglutinins and isoagglutinins after agglutination of the cells in the cold as well as in a few cases of atypical hemolytic anemia in which osmotic fragility was normal or decreased

Serologic Tests A simple presumptive test is performed by placing washed red corpuscles from fresh defibrinated blood in each of three test tubes The first is incubated for 1 to 2 hr at body temperature and then centrifuged If hemoglobin is present in the supernatant serum the presence of a *warm hemolysin* is suggested The second tube is chilled for 20 min in cracked ice then incubated for 1 hr and centrifuged If the result is positive the presence of a *cold hemolysin* is indicated The test tube should be examined before it has been warmed If only *cold agglutinins* are present and no hemolysins it will be seen that the red corpuscles agglutinate in the cold but fail to hemolyze when the tube is warmed the clumps disappearing instead When cold agglutinins are present one must be careful not to shake the cells too much while they are agglutinated in the cold since they may hemolyze and give a false cold hemolysin test The blood placed in the third tube is acidified with carbon dioxide If hemolysis is apparent after incubation for 1 hr and subsequent centrifugation *increased acid hemolysis* is suggested This test is positive in paroxysmal nocturnal hemoglobinuria

When positive results are obtained in any one of these tubes the test should be repeated with adequate controls and by the more complete procedures which are available Thus if a cold hemolysin appears to be present, the Donath Landsteiner test should be carried out

The *Coombs antiglobulin test* as already indicated has proved to be very valuable in helping to clarify the heterogeneous group of acquired hemolytic anemias The *direct" Coombs test* is carried out simply by mixing the patient s washed red cells with serum from rabbits immunized to human gamma globulin and examining the mixture for agglutination It serves to demonstrate the presence of "incomplete" antibodies that is those which are attached at some points on the surface of the red corpuscles and require a completing substance such an antihuman globulin to cause an agglutination reaction to take place A positive result has been observed in cases of idiopathic acquired hemolytic anemia in that type of paroxysmal cold hemoglobinuria which is associated with syphilis and in many instances of "symptomatic" hemolytic anemia The test has been negative in most cases of hereditary spherocytosis and is generally negative in sickle cell anemia and in paroxysmal nocturnal hemoglobinuria but in hemolytic anemia due to various physical or chemical agents it has sometimes been positive

A positive "direct Coombs test is also observed when isoimmunization to known immune bodies has occurred as in hemolytic disease of the newborn and in sensitization following transfusion The indirect test serves to differentiate such antibodies In the indirect test antihuman globulin serum is mixed with normal group O Rh positive and Rh negative red corpuscles which have been incubated in the patient s serum The resulting reactions are shown in Table 102 If agglutination occurs with both Rh positive and Rh negative cells Rh antibodies can be excluded

In performing the Coombs test it is important that potent antiserum be used and adequate controls carried out False negative results may occur if the red corpuscles have not been washed sufficiently or as a result of a prozone reaction due to inadequate dilution of the serum Cold hemagglutinins may cause a false positive reaction

The detailed elucidation of a case of hemolytic anemia of the antibody type will often require the use of still other procedures but these in the main are quite simple They include the setting up of agglutination tests at various temperatures and in several media such as isotonic sodium chloride solution and bovine albumin solution these are helpful in demonstrating and characterizing the ag

iron pigment are found in the liver kidneys and even lymph nodes

Symptoms Jaundice and splenomegaly are the most common manifestations and may pass un noticed for many years A persistent sallow appear ance rather than obvious jaundice may be present Symptoms of anemia are usually absent or mild At any time from birth to late adult life attention may be drawn to the disorder by the *crise de déglobu lisation* which is characterized by fever lassitude palpitation and shortness of breath or even violent abdominal pain vomiting and anorexia Rather than being episodes of increased blood destruction as has always been assumed these crises have been observed by several investigators to be associated with sudden temporary cessation of blood formation Since the life span of the red corpuscles of con genital hemolytic icterus is very brief anemia de velops rapidly under these circumstances It re mains to be shown how often such a mechanism rather than hemolysis is the cause of the crises which occur in this disease It has been suggested that both mechanisms play a role and that both are manifestations of hypersplenism"

The liver may or may not be enlarged Develop mental anomalies are often present A chronic leg ulcer may be found Cholelithiasis is a frequent complication and symptoms due to this cause may first bring the patient to the physician

The anemia is usually moderate in degree but may be very mild or severe It is normocytic or simple microcytic in type but when severe and as sociated with marked reticulocytosis it can be macrocytic There is little poikilocytosis but small bright deeply staining red corpuscles (spherocytes) are often seen scattered among the cells of normal size Reticulocytes are characteristically increased in number most often numbering 5 to 20 per cent Polychromatophilia and normoblasts may be seen in the blood smear The leukocytes are usually nor mal in number or slightly increased The platelet count is generally normal

Increased osmotic fragility of the red corpuscles is characteristic Hemolysis beginning at 0 64 per cent saline solution is not unusual and may be complete at the point where hemolysis normally begins

Bilirubinemia of the indirect type and increased quantities of urobilinogen in the urine and stools without bile in the urine (acholuric) are the characteristic changes in pigment metabolism

Diagnosis Splenomegaly icterus of the hemo lytic type reticulocytosis increased osmotic fragil ity and demonstration of the anomaly in other members of the family are the characteristic find ings The Coombs test is negative except in occa sional cases In these it is likely that a superimposed acquired immunohemolytic process has developed When the picture is not entirely typical a careful study to rule out other types of hemolytic anemia must be made as outlined previously

It is especially important to distinguish cases of *congenital nonspherocytic hemolytic anemia* be cause they have not been benefited by splenectomy Although such cases resemble hereditary sphero cytosis in their mode of inheritance they differ in that the anemia is generally macrocytic there is often a moderate degree of ovalocytosis and some times there is conspicuous punctate basophilia Spherocytes are not found and osmotic fragility is normal The reported cases have not been identical in all respects however and probably represent several different disorders This statement is based on observation of morphologic differences such as the presence of crenated and irregularly contracted corpuscles in some cases Pappenheimer bodies in others extreme variation in red cell size and shape in still others as well even as increased resistance to saline hemolysis and the presence of target cells as in instances of certain abnormal hemoglobin dis orders It has been shown that the reversibility of the metabolic lesion by adenosine observed in certain cases of hereditary spherocytosis did not occur in congenital nonspherocytic hemolytic ane mia Studies of autohemolysis have revealed at least two forms of the nonspherocytic disorder

Treatment This is the one disorder in which splenectomy is associated with consistently satis factory results The operation is indicated in every patient in whom clinical manifestations are present Although remissions develop and latent periods of many years duration may occur spontaneous recov ery does not take place At operation a careful search should be made for accessory spleens and they should be removed if found Following opera tion anemia jaundice and reticulocytosis disap pear The osmotic fragility of the red corpuscles however as well as the spherocytosis may persist

During a crisis repeated blood transfusions must be given

SICKLE CELL ANEMIA AND OTHER ABNORMAL HEMOGLOBIN SYNDROMES

Definition Sickle cell anemia is a hereditary and familial hemolytic anemia essentially peculiar to Negroes and characterized by the presence of red corpuscles which under appropriate conditions as sume sickle shaped or oat shaped forms

Etiology and Pathogenesis Just as hereditary spherocytosis is rare in the Negro sickle cell ane mia is extremely rare except in Negroes or when mixture with Negro blood has occurred The anom aly appears to be inherited as a mendelian dominant characteristic Inheritance of the abnormality from only one parent the heterozygous state is repre-

appear at any time from a few minutes to 7 or 8 hr following exposure

Donath and Landsteiner showed that the hemoglobinuria is due to the sudden intravascular hemolysis of blood as the result of the action of an autohemolysin contained in the patient's blood The hemolysin unites with the red corpuscles only at a low temperature but destruction of the corpuscles occurs only after the temperature of the blood has returned to body temperature Appropriate tests have been devised to demonstrate such a cold hemolysin At the time of hemolytic attacks produced by chilling strongly positive direct antiglobulin (Coombs) reactions have been observed but they become negative after the attacks The typical condition is a manifestation of syphilis the congenital form particularly and thorough antisyphilitic therapy ends the clinical manifestations

A number of cases have been described however in which indications of syphilis were lacking even though the Wassermann reaction was *positive* In view of the fact that false positive Wassermann and Kahn reactions are not uncommon in acquired hemolytic anemia of the autoantibody type it has been suggested that paroxysmal cold hemoglobinuria is not exclusively a manifestation of syphilis and that some of the cases regarded as the typical condition of syphilitic origin may well have been examples of autoimmune hemolytic disease of the cold antibody type

Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria (Marchiafava Micheli Syndrome)

This is a rare disorder of insidious onset which is characterized by signs of hemolytic anemia and is marked by attacks of hemoglobinuria which occur chiefly at night The symptoms are those of long standing anemia but there may be abdominal lumbar or substernal pain which often ushers in an attack of hemoglobinuria The findings are similar to those in other hemolytic anemias and include splenomegaly and well marked anemia The osmotic fragility of the red corpuscles is normal and spherocytosis is not characteristic There may be hemoglobinemia even when there is no hemoglobinuria Leukopenia is usual and may be marked and there may be thrombocytopenia The urine contains increased amounts of urobilinogen as well as hemoglobin Hemosiderin can often be demonstrated in the leukocytes or epithelial cells of the urine

The fault appears to reside in the red corpuscles which are unusually susceptible to acid hemolysis A simple test for this has been described already (p 1186) It has been suggested that the destruction of the cells is promoted by the accumulation of carbon dioxide during sleep an optimum acid pH being required for hemolysis to take place The latter has been shown to be brought about by the action of the *properdin system* The components of this system are properdin (a protein) Mg^{++} and cofactors resembling complement all of which are normal constituents of plasma Normal human red cells are not damaged by this system The defect in PNH (paroxysmal nocturnal hemoglobinuria) red corpuscles which renders them susceptible to the properdin system may possibly reside in the lipid pattern of the lipoproteins of their stroma

This disorder does not appear to be hereditary Treatment is purely symptomatic Splenectomy is of no value The intensity of the hemolytic process varies and crises of severe anemia may occur Transfusion of plasma usually precipitates hemolytic crises but fortunately saline washed red corpuscles can be given with impunity Although thrombocytopenia is common purpuric or hemorrhagic manifestations are unusual in fact thrombotic complications are not infrequent It has been found that *the anticoagulant dicoumarin (Dicumarol) impedes* hemolytic activity in this disease but this drug is chiefly of importance in order to prevent thrombotic complications Infections are frequent in these patients partly perhaps because of the associated leukopenia Prognosis varies greatly Although a fatal termination may ensue in several years in some cases the disorder has been compatible with life for many years

Hereditary Spherocytosis (Chronic Acholuric Jaundice Spherocytic Anemia Chronic Familial Icterus Congenital Hemolytic Jaundice)

Definition This is a familial and hereditary disorder characterized by spherocytosis increased osmotic fragility of the red corpuscles splenomegaly and a variable degree of hemolytic anemia

History Chiefly as the result of the observations of the French school during the early part of the present century this familial disorder was clearly defined becoming known as the type of Chauffard and Minkowski It was distinguished from the acquired form of hemolytic anemia of Hayem and Widal

Etiology Transmitted as a mendelian dominant by either parent this disorder is due to an inherited defect of the red corpuscles which tend to be more spheroid than normal and thus are more subject to destruction The significance of spheroidicity of the red corpuscles and of increased osmotic fragility and the role of the spleen have been discussed already (p 1184)

Morbid Anatomy The spleen is greatly enlarged often weighing 1 000 to 1 500 Gm The pulp and to a lesser extent the sinuses are greatly congested Depending on the degree of anemia and the extent of blood destruction hyperplasia and even metaplasia of the bone marrow occur and deposits of

Table 103 USUAL FINDINGS IN ABNORMAL HEMOGLOBINOPATHIES AND THALASSEMIA

Condition	Hb types[1]	Sickling	Microcytosis	Hypochromia	Target cells[2] per cent	Hemolytic anemia[3]	Splenomegaly
Normal—adult	AA	0	0	0	0	0	0
Normal—newborn	AF	0	0	0	0	0	0
Trait							
Sickle-cell trait	AS	+	0	0	4	0	0
Hb C trait[4]	AC	0	0	+	0–40	0	0
Hb D trait	AD	0	0	0	?	0	0
Hb E trait	AE	0	0	0	2	0	0
Hb G trait[4]	AG	0	0	0	0	0	0
Hb H trait (?)	AH	0	+	+	+	++	++
Hb I trait	AI	0	0	0	<2	0	0
Disease							
Sickle-cell anemia	SS	++	0	0 +	5–30	++++	0
Homozygous Hb C	CC	0	±	+	40–100	++	++
Homozygous Hb E	EE	0	++	0	25–60	+[7]	±
Homozygous Hb G	GG	0	0	0	0	0	0
Sickle-cell Hb C[5]	SC	+	±	+	20–85	++	++
Sickle-cell-Hb D[6]	SD	+	+	+	±	++	++
Sickle-cell Hb G	SG	+	0	0	0	0	0
Thalassemia minor	AA	0	±	±	+	+	±
Thalassemia major	AF	0	++	++	10–35	+++	++++
Sickle-cell thalassemia	SF	+	+	+	20–40	++	++
Hb C thalassemia	CA	0	+	±[8]	+++	+	0
Hb E thalassemia	EF	0	+	+[8]	10–40	+	++
Hb G thalassemia (?)	GF	0	+	+	+	+	0
Sickle-cell hereditary spherocytosis	SA	+	+	0	+	++	++

[1] The major hemoglobin component is shown first. In sickle-cell anemia especially there may also be a substantial proportion of Hb F.
[2] Osmotic fragility is reduced more or less proportionately to the number of target cells.
[3] Mechanical fragility and RBC survival correspond *as a rule* to the presence and degree of hemolytic anemia.
[4] Chiefly in Negroes.
[5] Cases of sickle-cell anemia intermediate in severity between sickle-cell trait and sickle-cell anemia.
[6] Sickle-cell disease in Caucasians.
[7] Or polycythemia with microcytosis.
[8] Basophilic stippling of the red corpuscles.
SOURCE Wintrobe, Clinical Hematology, 4th ed, Philadelphia, Lea & Febiger, 1956.

with S hemoglobin is accompanied by sickling of the red corpuscles as well as by a hemolytic syndrome similar to sickle cell anemia but differing in that the hemolytic anemia is milder, target cells are more plentiful in the blood, and there is slowly progressive splenomegaly. It is very probable that most of the cases formerly reported as representing forms of sickle cell anemia intermediate between the asymptomatic carrier state and the homozygous classical disease actually were cases simultaneously heterozygous for S and C hemoglobin.

Hemoglobin D is very rare. *Hemoglobin E* has been found in approximately 13 per cent of the population of Thailand and has been encountered frequently in association with the gene for thalassemia. *Hemoglobin G* has been found in Negroes in West Africa and in a family of Italian origin. *Hemoglobin H* was described in a Chinese family and in a Greek family and has also been observed in Thailand. *Hemoglobin I* has been identified in a Negro family. *Hemoglobin J* and *K* have also been reported. In Table 103 some of the hematologic characteristics associated with the inheritance of the various abnormal hemoglobins are indicated and the clinical manifestations associated with the homozygous states and various gene combinations are also outlined.

Sickle cell anemia was first described in Negroes

sented by the sickle cell trait in which sickling of the red corpuscles can be demonstrated but is not accompanied by symptoms of anemia Sickle cell anemia is the homozygous state in which one abnormal gene has been inherited from each parent Sickle cell anemia possesses all the characteristics of a chronic hemolytic anemia with certain special features as well

From time to time exception has been taken to the heterozygous homozygous theory described above because of certain family studies which failed to demonstrate the sickle cell trait in both parents of children with sickle cell anemia and also because certain cases were observed which seemed to be intermediate in their clinical manifestations between those of the severe hemolytic anemia of sickle cell anemia and the asymptomatic state the sickle cell trait The discovery of abnormal hemoglobins other than sickle cell hemoglobin has offered a reasonable explanation for these exceptions as will be described shortly

The discovery by Pauling and his associates that the electrophoretic mobilities of sickle cell anemia (S) and normal hemoglobin (A) differ led to establishment of the principle that a molecular abnormality in a single protein may cause a sequence of events such as that which characterizes the complex disease sickle cell anemia It was shown that in a buffer of suitable pH the two components of a mixture of normal and sickle cell hemoglobin migrate in opposite directions On the basis of the difference in their isoelectric points it was concluded that the hemoglobin of sickle cell anemia has two to four more net positive charges per molecule than normal hemoglobin Since the heme moiety is the same in sickle cell and in normal hemoglobin the electrophoretic differences have been attributed to differences in the folding or coiling of the polypeptide chains thus either bringing into play or removing from action charged groups and thus indirectly altering the electrophoretic behavior of the proteins

The ratio of sickle cell hemoglobin to normal hemoglobin in the blood of individuals with the sickle cell trait has been found to vary from 22 to 45 per cent while the amount in the blood of those with sickle cell anemia has varied from 76 to 100 per cent The variations in the amount of sickle cell hemoglobin have been explained on the ground that the expression of the S gene may be under the modifying influence of other genetic factors the lower and higher proportions of S hemoglobin are a familial characteristic

Hemoglobin S is relatively insoluble The sickling process seems to be best explained on the assumption that in the oxygen unsaturated state the S hemoglobin molecule undergoes orderly orientation forming by specific linkage of the individual molecules long chains of hemoglobin elements Subsequent parallel alignment of these elements results in birefringent tactoids the sickled cell being a hemoglobin tactoid thinly veiled and somewhat distorted by the cell membrane The clinical and hematologic manifestations and the pathologic changes found in sickle cell anemia can be explained by the peculiar physical properties of the sickle cell The intracellular molecular orientation produces the sickled form of the erythrocyte At decreased oxygen tensions the viscosity of the whole blood and the mechanical fragility of the erythrocytes are significantly increased owing to the assumption of the sickled form With the increase in viscosity a cycle is initiated in which the factors of stasis lowered pH and continuing oxygen uptake combine to augment the number of sickled cells and prolong the stasis Plugs or masses of sickled erythrocytes become solid enough to occlude vessels and result in the "thrombotic episodes associated with pain which are characteristic of the disease Erythrostasis limits access to cell maintaining energy and also favors the sickled state When red cells after stasis are released into free circulation a certain proportion having been fixed in irreversible sickled form have also become more fragile in terms of mechanical trauma Consequently they are more than normally susceptible to the trauma associated with circulation Increased blood destruction is the result The development of these changes depends on the quantity of abnormal hemoglobin present it is assumed that in the homozygous state the erythrocytes contain sufficient abnormal hemoglobin to result in sickling within the physiologic range of oxygen tensions It is of interest that although the heterozygous state is ordinarily benign splenic infarction has been observed in a number of instances in persons with the sickle cell trait who were subjected to conditions of greatly reduced oxygen tension

Hemoglobin C is the name given to a third type of adult hemoglobin so named to distinguish it from *hemoglobin A* normal adult hemoglobin and *hemoglobin S* sickle cell hemoglobin The incidence in the United States of the gene responsible for C is about 2 per cent in the Negro population as compared with about 9 per cent for S hemoglobin

Carriers of hemoglobin C are asymptomatic but target red corpuscles are found characteristically in their blood The homozygous (CC) state is characterized by the presence of a normocytic hemolytic anemia of mild degree or no anemia whatsoever More than two dozen instances of homozygous hemoglobin C disease have been reported all in Negroes with but two exceptions

In addition a number of instances have been discovered in which both S and C hemoglobin were demonstrated The combination of hemoglobin C

Etiology Those first discovered to be affected were chiefly of Italian Greek Syrian or Armenian parentage In certain communities of Italians the anomaly has been observed in as many as 4 per cent of those examined The disorder is due to the inheritance of a factor which leads to an anomaly of red corpuscle production While there is in this condition a disturbance in iron metabolism the primary defect appears to be in hemoglobin synthesis It has been found that the red corpuscles in this disorder contain a variable and often large proportion of fetal hemoglobin as indicated by the high resistance of the hemoglobin to denaturation in aqueous alkaline solutions as well as by other physical properties In the severe form of the disease the electrophoretic pattern of the hemoglobin resembles a mixture of normal and fetal hemoglobin This has led to the suggestion that the gene governing this disorder blocks the production of normal hemoglobin and causes the production of fetal hemoglobin as a compensatory phenomenon The mode of inheritance seems to be that of a recessive In the heterozygous state when only one allele is inherited (thalassemia minor) the interference with hemoglobin synthesis is not serious In the homozygous condition when two alleles are inherited one from each parent (thalassemia major) there is a drastic reduction in normal hemoglobin production

The discovery of the high incidence of thalassemia in Thailand where it is said to be the most common form of hemolytic anemia and the report of thalassemia minor in the Sikh community in Vancouver Canada as well as in the Chinese and other Orientals has led to the suggestion that the thalassemia trait was carried from a large area in the Mediterranean Basin along the routes of the early migration of races

Symptomatology The full blown disorder (*thalassemia major Cooley s anemia*) develops insidiously within the first year or two of life perhaps at birth and is marked by pallor and great enlargement of the spleen and even the liver The appearance of the child is often mongoloid Roentgenograms reveal great thickening of the diploe of the skull with perpendicular striation increase in the medullary portion of the long bones with thinning of the cortex and other changes attributable to the extreme hyperplasia of the bone marrow Anemia is severe hypochromic and microcytic in type and the red corpuscles contain so little pigment and are so thin that their "buckling produces forms which have the appearance of targets Fragility tests in hypotonic saline solutions reveal that the corpuscles are unusually resistant to hemolysis by this means Normoblasts and microblasts as well as polychromatophilia basophilic stippling Howell Jolly bodies and moderate reticulocytosis in addition to leukocytosis (19 000 to 25 000 per cubic millimeter) with "shift to the left reflect the myeloid hyperactivity There is usually slight or moderate bilirubinemia with a corresponding increase in the urobilinogen content of the urine and stools

Thalassemia minor on the other hand may pass entirely unnoticed since painstaking examination may be necessary to reveal any abnormality Slight anemia splenic enlargement microcytosis and hypochromia target cells poikilocytosis out of proportion to the existent anemia decreased hypotonic saline fragility basophilic stippling of the red corpuscles and bilirubinemia are some of the signs which singly or in various combinations mark this disorder Roentgenographic changes in the bones similar to though less pronounced than those found in the severe form may be observed

The degree of penetrance of the thalassemia gene seems to vary greatly or there are modifying factors There is such a wide range in the manifestations of the heterozygous condition that some investigators have attempted to classify the Mediterranean hemopathic syndrome in a number of different groups The term *thalassemia minima* refers to those instances in which the manifestations are very slight In some persons the number of red corpuscles is actually increased above normal although since the red corpuscles are usually microcytic and hypochromic the hemoglobin and volume of packed red cells are usually slightly below the average normal values

Microdrepanocytic disease is the name given to the combination of sickle cell and thalassemia genes which results in a chronic hemolytic anemia with some of the characteristics of both sickle cell disease and thalassemia The thalassemia trait has also been observed in association with hemoglobin C hemoglobin E and other hemoglobins Some of the clinical and hematologic manifestations of these combinations have been outlined in Table 103

Diagnosis Plumbism congenital hemolytic jaundice and sickle cell anemia are among the disorders which must be distinguished on the basis of the characteristics already described

Prognosis The severe form is fatal and seems to be more grave the earlier it becomes manifest Less severe forms are compatible with life and the mildest forms may even have no influence whatever on life span

Treatment With the exception of the rare forms of hypochromic microcytic anemia which were discussed earlier (p 1174) this is the only form of hypochromic microcytic anemia in man which does not respond to iron therapy Splenectomy is of no value nor are any other measures now known

Pathology Evidences of pronounced myeloid hyperplasia both medullary and extramedullary the effects of such changes on the bones and de

in North America In Africa there is a broad belt of high incidence of the sickling trait which extends roughly across the middle third of the continent the highest figures being in eastern and central Africa The sickling trait however does not seem to be present exclusively in the Negroes of Africa or in Negroes of African origin It has been discovered in certain aborigines in southern India and in southern Arabia as well as in Greece and in southern Turkey However the homozygous condition sickle cell anemia is very rare in the white race Instances of sickle cell anemia which have hitherto been described in white persons have been in those of Greek or Italian stock These cases it now appears are examples of admixture of the sickling and the thalassemia traits and are not instances of the homozygous sickle cell disease

Pathology In addition to the signs of a chronic *hemolytic anemia (normoblastic hyperplasia of the* bone marrow hemosiderosis) evidence of thrombosis infarction necrosis) or hemorrhage may be present especially in the lungs spleen and nervous system The spleen may be shrunk to a tiny wrinkled mass

Symptoms Jaundice and a chronic anemia with few or no complaints are interrupted by periods of increased weakness episodes of aching pain in the joints or elsewhere in the extremities or sudden attacks of severe abdominal pain which have often been mistaken for ruptured peptic ulcer intestinal obstruction or some other abdominal emergency

The victims of sickle cell anemia are often poorly developed and bony deformities of various types may be discovered The scleras are icteric and there may be slight general glandular enlargement but splenomegaly is encountered in only about 15 to 20 per cent of cases The heart may be enlarged and the physical signs may closely simulate those of mitral stenosis due to rheumatic fever Hyposthenuria is common In many instances chronic leg ulcers are found over the internal or external malleoli Roentgenograms may reveal radial striation in the skull osteoporosis in the vertebral bodies or other changes in the long bones Osteomyelitis is a not infrequent complication

The anemia is usually surprisingly severe erythrocyte counts below 2 5 million being common The anemia may be normocytic or macrocytic Oval cigar shaped or other bizarre forms of red corpuscles may be seen in the stained blood smear The sickling is brought out clearly in wet films of blood which have been fixed under a cover glass and sealed with paraffin In cases with sickle cell anemia the typical sickled and oat shaped forms with elongated pointed filaments appear within a few hours When only the sickle cell trait exists 24 hr is often required to produce *this change* and only a proportion rather than practically all of the cells are affected By the use of reducing agents such as sodium bisulfite sickling can be hastened and the characteristic forms appear promptly

In sickle cell anemia reticulocytosis polychromatophilia normoblasts leukocytosis with shift to the left" in the myeloid series and an increase in platelets are found as well as hyperbilirubinemia and increased urobilinogen in the urine and stools Osmotic fragility is decreased not increased The bone marrow shows striking normoblastic hyperplasia

Diagnosis Sickle cell anemia is often mistaken for some other disease *Rheumatic fever* peptic ulcer renal or biliary calculus osteomyelitis and various neurologic disorders may be simulated Recognition depends on the demonstration of sickling and the finding of anemia of the hemolytic type

In distinguishing persons with the sickle cell trait who may have some disorder accompanied by anemia from those who have sickle cell anemia it must be kept in mind that the former may develop any type of anemia while in the latter the anemia is always hemolytic in type

The distinguishing features of the other hemoglobinopathies and of disorders resulting from combinations of the sickle cell gene with the genes for other abnormal hemoglobins or with the thalassemia gene are presented in Table 103 For the exact identification of the abnormal hemoglobins paper electrophoresis and the alkali denaturation procedure for fetal hemoglobin are necessary

Treatment There is no satisfactory treatment Splenectomy is of no value Blood transfusion may be helpful in the abdominal crisis if shock is present The disease is ultimately fatal often before the age of thirty

THALASSEMIA (Cooley s Anemia Erythroblastic Anemia Mediterranean Anemia Target-cell Anemia Familial Microcytic Anemia)

Definition An inherited disorder seen particularly in individuals living in countries bordering the Mediterranean or in their offspring elsewhere which is characterized by the presence of unusually thin red corpuscles microcytosis various degrees of anemia and when the anemia is severe numerous nucleated red corpuscles There is also a high incidence in Thailand

History Cooley and Lee (1925) described a chronic progressive anemia commencing early in life which was associated with a *characteristic* facies splenomegaly and a *familial and racial* incidence Later it became clear that this was the *severe* and fatal form of a disorder which in milder form is seen in adolescents and in adults

As already described the anemia of *iron deficiency* is hypochromic microcytic in type and that due to lack of anti pernicious anemia principle and related substances is macrocytic *Protein deficiency* is characterized by the presence of normocytic anemia Deficiencies of the various B vitamins are rarely encountered in man in pure form Multiple nutritional deficiencies are associated as a rule with only moderate anemia usually normocytic in type

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posits of iron containing pigment in the liver pancreas and other tissues are the most significant findings

ANEMIAS ASSOCIATED WITH INFECTIONS AND VARIOUS OTHER DISORDERS CHIEFLY CHRONIC

In the preceding sections anemia resulting from blood loss as well as anemias due to excessive blood *destruction* and *those associated with deficiency* of certain factors concerned in erythropoiesis were discussed The characteristics of these anemias are in the main well defined and much has been learned in recent years about their pathogenesis The hemolytic anemias and the specific nutritional deficiency anemias are however relatively uncommon Far more frequent in occurrence and yet *much less well understood are the anemias associated* with various chronic disorders and with infection Such anemia is usually only moderate in degree hemoglobin values of 13 to 10 Gm per 100 ml of blood are seen more frequently than lower values The anemia is usually normocytic and in the smear the red corpuscles generally show little abnormality in size or shape a monotonous picture unaccompanied by polychromatophilia basophilic stippling or nucleated red corpuscles Exceptions are found in *lead poisoning* where basophilic stippling *is characteristically seen* in the so called *myelophthisic anemias* such as those associated with metastases to the bone marrow leukemia multiple myeloma or myelosclerosis and in severe *renal disease* There often corresponding rather closely to the gravity of the renal disorder as manifested by the degree of retention of nitrogenous and other waste products hemoglobin values as low as 5 Gm per 100 ml are found and the blood smear may reveal normoblasts stippling and moderate anisocytosis and poikilocytosis The anemia may be somewhat microcytic or hypochromic and occasionally is macrocytic If the renal disease has been insidious in onset and is chronic in type the clinical manifestations and the anemia may be quite confusing unless one is aware that striking degrees of anemia may be encountered in the absence of impressive signs of renal disorder

The *bone marrow* in these conditions shows nothing characteristic The nucleated red corpuscles are of the normoblastic type The marrow may appear hyperplastic normal or hypoplastic *Hyperplasia of the leukopoietic* tissue is found if the disorder is one which calls forth a leukocytic response

The *pathogenesis of the anemia in these conditions* has been discussed elsewhere (p 201) It seems likely that some fault in the construction of red corpuscles is an important *underlying mechanism* in their development In any event the impact of infection on erythropoiesis is such that no form of antianemic therapy such as the administration of vitamin B_{12} or of iron has any influence The anemia disappears spontaneously if the infection is successfully treated or subsides as the result of the defense reactions of the host Similarly *the anemia of renal insufficiency is closely tied with* the underlying disorder and is generally not influenced by measures other than those which affect *renal function*

It is both interesting and curious therefore that the oral administration of *cobaltous chloride* in doses ranging from 20 to 160 mg per day generally in the form of 20 mg size enteric coated tablets taken with meals has been observed to produce a modest reticulocytosis and a significant moderation in the degree of anemia both in cases of anemia *accompanying chronic infection* and *in that associated* with renal disease In the latter appetite may improve and there may be increased tolerance for the medications necessary to correct electrolyte abnormalities There is no evidence that cobalt therapy alters the course of renal disease and the hemoglobin has been found to return to pretreatment levels after cobalt administration has been discontinued *The mode of action of cobalt is obscure* but it is generally assumed that it serves as a nonspecific erythropoietic stimulant rather than as a specific nutritional component required for red cell or hemoglobin production

Malignant disease is not necessarily accompanied by anemia Anemia accompanies malignancy in the alimentary tract more often than elsewhere In such cases nutritional deficiency may play an important role in the pathogenesis of the anemia and in many cases blood loss is also a contributory factor Malignant disease of the kidneys breast prostate thyroid and lungs in particular may metastasize to bones and in such an event "*myelophthisic anemia* may develop *The picture then may be that of* a pancytopenia (see p 1210) or a leukemoid picture may result The latter is marked by leukocytosis together with a moderate *shift to the left* in the leukocytic formula and normocytic anemia When a number of nucleated red corpuscles also appear in the peripheral blood as they sometimes do the term *leukoerythroblastic* anemia appropriately describes what is found The pathogenesis of myelophthisic anemia was discussed briefly elsewhere (p 202)

Endocrine insufficiency may be associated with anemia Hypothyroidism is often accompanied by anemia of moderate degree This is usually normocytic but can be macrocytic (p 210) Slight or moderate anemia usually normocytic is found in Addison s disease and in pituitary insufficiency (*Simmonds disease*)

History Vaquez in 1892 described a case of polycythemia which he had originally attributed to congenital heart disease Osler gave a more complete description in 1903

Etiology and Pathogenesis None of the recognized causes of erythrocytosis already discussed in Chap 12 (p 98) appears to play a role in this disorder It appears usually in middle or late life Familial cases have been described

Since oxygen want is known to produce polycythemia hypoxemia of the bone marrow has been proposed as the fault underlying the development of erythremia Not only is there no demonstrable bone marrow hypoxia in erythremia but this hypothesis ignores the fact that the increase in red corpuscles is but a part of a generalized myeloid hyperplasia which may be manifested in leukocyte counts as high as 60 000 per cubic millimeter and an increase in platelets A close relationship to chronic myelocytic leukemia is suggested by such cases A failure of hematopoietic balance can also be postulated but unfortunately the factors which regulate and maintain the blood at "normal" are unknown

Pathology The striking changes are those related to the increase in total blood volume All the organs are engorged with blood the veins stand out like bunches of thick worms and there may be thromboses or anemic infarcts The *bone marrow* is dark red in color and very cellular Microscopically this is found in most instances to be due to hyperplasia of all the marrow elements In some cases the percentage of normoblasts is increased in others the proportions of myelocytes and myeloblasts or of basophilic and eosinophilic cells may be greater than normal

The *spleen* is enlarged chiefly from hyperplasia of the pulp and distention with blood Infarcts are common There may be foci of extramedullary blood formation in the spleen the liver and occasionally elsewhere as well Cirrhosis of the liver has been observed in a number of instances

Symptomatology The onset is insidious and the progress gradual Headache dizziness ringing in the ears or visual disturbances dyspnea lassitude or weakness skin or mucous membrane hemorrhages a sense of weight in the abdomen due to the enlargement of the spleen or irritability depression forgetfulness or vague symptoms suggesting neurasthenia are complaints encountered in many cases Various gastrointestinal symptoms such as fullness belching or constipation may be present or symptoms of peptic ulcer may be found Sometimes the symptoms are those attributable to increased metabolism lassitude increased sweating and loss of weight Swelling and pain in the extremities may be very troublesome In still other cases the symptoms are so insignificant that the polycythemia is discovered only accidentally

The face is a deep red rather than truly cyanotic The color is most noticeable in the lips cheeks tip of the nose ears and neck The distal portions of the extremities may be more truly cyanotic since the highly viscous blood circulates more sluggishly there than is normal Ecchymoses are common and epistaxis and bleeding of the gums are frequently encountered Cardiac abnormality is unusual but vascular disturbances are common These include venous thromboses coronary thrombosis and cerebrovascular accidents The blood pressure is more often normal than elevated Enlargement of the liver is frequent and splenomegaly is found in at least 75 per cent of cases The spleen may be just palpable or it may extend even to the pelvic brim

Blood Erythrocyte counts of 7 to 10 million cells per cubic millimeter are common Unless hemorrhage has occurred or venesections have been performed there is a corresponding increase in hemoglobin and in volume of packed red corpuscles The individual red corpuscles appear normal although occasional polychromatophilia or basophilic stippling may be noted The finding of nucleated red corpuscles and the appearance of small numbers of myelocytes and even earlier forms in the blood give a clue to the hyperplastic state of the bone marrow leukocytosis sometimes of marked degree (60 000 per cubic millimeter) due to an increase of the granulocytes and high platelet counts when present give further evidence of overactivity The percentage of reticulocytes is not increased unless there has been recent bleeding The osmotic fragility of the red corpuscles is not significantly altered There may be some evidence of increased blood destruction in the form of slight bilirubinemia and increased excretion of urobilinogen The viscosity of the blood is greatly increased even five to tenfold The thick sticky blood may be slow to coagulate and the clot may not retract Bleeding and clotting times are usually normal however

The total blood volume is substantially increased (150 to 300 per cent of normal) entirely because of an increase in red corpuscle mass

Other Laboratory Findings These include increased basal metabolic rate in many cases normal increased or reduced gastric secretion even achlorhydria and normal urine or slight proteinuria

Diagnosis The symptoms of erythremia alone may suggest a variety of disorders but once the blood has been examined the problem is to differentiate secondary forms of polycythemia (*erythrocytosis*) from the primary disorder (see p 99) Failure to discover a cause for the polycythemia and the presence of a reddish rather than bluish cyanosis favor the diagnosis of erythremia

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213 ERYTHREMIA (Polycythemia Rubra Vera)

M M Wintrobe

Definition Erythremia also known as Vaquez or Osler s disease or splenomegalic polycythemia is a disease of unknown etiology and of insidious onset and slow chronic course It is characterized by a striking absolute increase in the quantity of circulating red corpuscles and often by evidence of increased production of myeloid leukocytes and even of platelets Splenomegaly and a red cyanosis of the skin as well as increase in the viscosity of the blood and in the total volume of the blood are additional features of this disorder

as soon as it is formed The exact nature of this mechanism is not understood

Etiology *Hereditary* or *familial methemoglobinemia* is a rare condition approximately 100 cases have been reported in the literature The mode of inheritance is unknown Both sexes are affected although there is a preponderance of male victims All the families described have been of the white race and individuals of Greek stock have predominated Cyanosis without associated clubbing of the fingers is present from birth and methemoglobin comprises 20 to 50 per cent of the total hemoglobin A compensatory polycythemia is frequently observed The disease is rarely fatal and most of the patients reach an advanced age A number of patients with *congenital methemoglobinemia* have been reported without a familial history of the disease and a few patients with *idiopathic methemoglobinemia* have been observed in whom the congenital nature of the disease was not clearly demonstrated In patients with one of the above forms of methemoglobinemia the normal cellular mechanism for reducing methemoglobin is absent

Secondary methemoglobinemia is more common than hereditary or congenital methemoglobinemia and is caused by contact with drugs containing amino or nitro groups (Table 104) These drugs preferentially oxidize hemoglobin and in sufficient amounts overcome the normal reducing mechanism of the erythrocytes In secondary methemoglobinemia unlike what happens in the hereditary or congenital forms of the condition the oxygen dissociation curve is shifted to the left and the unloading of oxygen in the tissues is seriously handicapped (Chap 12) When exposure to the offending drug ceases the methemoglobin is rapidly converted to the reduced compound and the cyanosis disappears Nitrates after ingestion may be converted to nitrites by intestinal bacteria and after absorption from the intestine produce methemoglobin Cases of methemoglobinemia due to nitrates or nitrites have been reported following the use of bismuth subnitrates or of ammonia or potassium nitrate from the therapeutic use of amyl nitrite or nitroglycerin from food high in nitrates in infants drinking well water high in nitrates from the inhalation of nitrous gases by arc welders and by the ingestion of corning syrup Aniline dyes may produce methemoglobinemia by penetration of the infant skin Contact with dyed blankets laundry marks on diapers and freshly dyed shoes has produced methemoglobinemia The ingestion by children of certain red wax crayons containing p nitroaniline has resulted in methemoglobinemia The commonly dispensed analgesic and antipyretic drugs acetanilid and phenacetin are aniline derivatives and have frequently been found responsible

Table 104 AMINO AND NITRO COMPOUNDS PRODUCING METHEMOGLOBINEMIA

Aromatic drugs	*Aliphatic and inorganic drugs*
Aniline	Sodium nitrite
Aminoethanol	Hydroxylamine
Phenacetin	Dimethylamine
Acetanilid	Nitroglycerin
Methylacetanilide	Amyl nitrite
Hydroxylacetanilid	Ethyl nitrite
Prontosil	*Bismuth subnitrate*
Sulfanilamide	Ammonium nitrate
Sulfathiazol	*Potassium nitrate*
Sulfapyridine	
Phenylenediamine	
Aminophenol	
Toluenediamine	
Alpha naphthylamine	
Para aminopropiophenone	
Phenylhydroxylamine	
Tolylhydroxylamine	
Nitrobenzene	
Dinitrobenzene	
Trinitrotoluene	
Nitrosobenzene	
Para nitroaniline	

SOURCE C A Finch Methemoglobinemia and Sulfhemoglobinemia New Engl J Med 239 470 1948

for methemoglobinemia Certain sulfonamides such as sulfanilamide Prontosil sulfathiazole and sulfapyridine but not sulfadiazine or sulfamerazine produce the condition

Enterogenous cyanosis is a term used to refer to a clinical syndrome characterized by attacks of cyanosis headache abdominal pain with either diarrhea or constipation dyspnea dizziness collapse and syncope Many of the patients reported were taking aniline derivatives for headache It has been suggested that because of the gastrointestinal disease there was an abnormal production and absorption of nitrites Sulfhemoglobinemia has been present frequently together with methemoglobinemia in the blood of these patients

In addition to the above types of methemoglobinemia rare cases of acquired hemolytic anemia with paroxysmal methemoglobinemia have been reported

Clinical Manifestations When as little as 1 5 Gm of methemoglobin is present in 100 ml of blood recognizable cyanosis results In contrast about 5 Gm of reduced hemoglobin must be present before a comparable degree of cyanosis occurs Since methemoglobin is incapable of combining with oxygen the symptoms of methemoglobinemia are attributable to the hypoxia produced by the lowered oxygen capacity of the blood The severity of the

Splenomegaly is very unusual in erythrocytosis even when the erythrocyte count is very much increased What is more in the latter condition leukocytosis immature leukocytes and an increase in the platelet count are hardly ever found and normoblasts are much more uncommon in the blood than in erythremia

An absolute increase in red corpuscle mass is found in erythrocytosis as well as in erythremia Measurement of blood volume therefore does not aid in differentiating secondary polycythemia but because of variations in plasma volume it is a truer index of the degree of polycythemia than the hematocrit level It is also helpful in the occasional patient often a heavily built middle aged and sometimes hypertensive male in whom there is only relative polycythemia (stress erythrocytosis) Measurement of arterial oxygen saturation is useful in differentiating erythrocytosis due to cardiac or pulmonary disease for in the latter oxygen saturation is reduced more or less in inverse proportion to the degree of polycythemia whereas in erythremia it is normal or nearly normal

Course and Complications Barring the development of serious complications the course of erythremia adequately treated is chronic and the disorder is often compatible with many years of life The most dangerous complications are vascular thrombosis or hemorrhage Therapy by keeping the red corpuscle mass at a nearly normal level can effectively reduce blood viscosity and thus serves to reduce the likelihood of such vascular accidents Intercurrent infections especially of the respiratory tract may be troublesome and bronchitis and emphysema may develop Peptic ulcer and hypertension are frequent complications and less often gout and cirrhosis of the liver The development of typical chronic myelocytic leukemia in a number of cases of erythremia has given support to the view that there may be a close relationship between these two disorders

Treatment Treatment is symptomatic since the cause of erythremia is unknown Symptomatic relief is best achieved by reducing the red corpuscle mass to something approaching normal This is most quickly achieved by *venesection* Approximately a pint of blood is removed twice a week or even more often until the volume of packed red corpuscles approaches normal Then the procedure may need to be repeated only once a month or less often *Phenylhydrazine hydrochloride* though now rarely used is effective in destroying the red corpuscles but it is best first to use venesection to lower the blood level to normal subsequently giving only enough of the hemolytic agent to maintain the blood at normal For this purpose 0 1 Gm in capsules once a day every other day or every third day should be adequate The use of such small doses will avoid complications of phenylhydrazine therapy such as thrombosis and acute hemolytic anemia This drug should not be used for bed ridden patients or for those who have thrombosis already

Instead of removing or destroying the excessive red corpuscles hematopoiesis may be inhibited by irradiation or by nitrogen mustard therapy The effects of *irradiation* are slow to appear however and consequently venesection must be used at the same time initially The *intravenous injection of* radioactive phosphorus (P^{32}) is more satisfactory than roentgen therapy The procedure depends on the fact that the radioactive phosphorus passes to tissues which have a high phosphorus content The concentration of P^{32} in the bones places this agent in a strategic position Usually 3 to 5 millicuries of P^{32} is given After 10 to 12 weeks if symptomatic and hematologic improvement are inadequate a second dose is administered Subsequent therapy is "titrated" according to need but intervals between injections should not be shorter than 10 weeks and leukocyte and platelet counts should be included in the blood examinations as guides in avoiding marrow aplasia from overdosage Remissions of 6 to 10 months are common but much longer ones are not unusual

Although agents such as nitrogen mustard and triethylenemelamine have been shown to be effective in the treatment of erythremia they offer no advantages over radioactive phosphorus while their toxic effects scarcely justify their use if P^{32} is available

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214 METHEMOGLOBINEMIA, SULFHEMOGLOBINEMIA

George E Cartwright

METHEMOGLOBINEMIA

Methemoglobin is an oxidation product of hemoglobin which cannot function as an oxygen carrier Under normal circumstances 98 to 99 per cent of the hemoglobin in the erythrocytes is in the reduced state (ferrohemoglobin) and 1 to 2 per cent is in the oxidized state (ferrihemoglobin or methemoglobin) The reduced hemoglobin is constantly being converted to methemoglobin but some mechanism within the cells reduces the methemoglobin

215 THE PURPURAS

M M Wintrobe

Definition The term *purpura* refers to extravasations into the skin or mucous membranes They may vary from the size of a pin point or slightly bigger (petechiae) to much larger areas (ecchymoses) Purpura is but one manifestation of abnormal bleeding already discussed (p 214)

THROMBOCYTOPENIC PURPURA

Definition This term refers to purpura which is accompanied by a significant reduction in the platelet count There is at the same time prolongation of bleeding time a positive tourniquet test and poor clot retraction but the coagulation time and prothrombin time are normal The purpura may be *essential* or *primary* this also being known as *purpura hemorrhagica* or *Werlhof's disease* or it may be symptomatic the effect of various chemical vegetable animal or physical agents the accompaniment of certain infections or a part of the picture of various blood disorders

History Werlhof in 1735 distinguished purpura hemorrhagica as an entity distinct from the purpuric manifestations of various pestilential fevers and differing from other hemorrhagic disorders Denys noted the thrombocytopenia in 1887 while Kaznelson proposed treatment by splenectomy in 1916

Etiology and Pathogenesis Purpura hemorrhagica occurs most frequently in children and in young adults and is somewhat more common in the female than in males No more than 10 per cent of cases begin after the age of forty Not infrequently there is a family history of excessive bleeding The condition is rare in Negroes

In the bone marrow the number of megakaryocytes is normal or may even be increased However in contrast to the normal picture few or no platelets are found about their margins Moreover also significant is the fact that splenectomy is often followed by striking improvement These observations have led to the assumption that this disorder is caused by (1) a decreased rate of formation of platelets from megakaryocytes as the consequence of splenic inhibition (2) platelet destruction by the spleen or (3) a combination of damage to both megakaryocytes and circulating platelets perhaps through the action of a humoral factor in the plasma That the last is true in many cases probably as the result of an immunologic mechanism is indicated by studies in which platelet agglutinins were shown to be present in the plasma of patients with essential thrombocytopenic purpura It was also demonstrated that the injection of plasma from patients with this disease into normal recipients was associated with thrombocytopenia bleeding phenomena and alterations in the megakaryocytes Furthermore transfused platelets disappear with extraordinary rapidity from the circulation of patients with acute idiopathic thrombocytopenic purpura It is plausible to assume that the spleen removes sensitized platelets and may also produce some of the platelet agglutinin

Platelet agglutinins were first described in patients with thrombocytopenic purpura due to Sedormid In these cases it was shown that the drug forms an antigenic complex with the platelets to which an antibody is formed It is possible that in "idiopathic" thrombocytopenic purpura an unidentified toxin affects both platelets and capillary endothelium which are antigenically similar and that an antibody to these damaged tissues is produced

That there is in addition to thrombocytopenia a defect in the capillary endothelium is suggested by the fact that hemorrhage in this disease is not always closely correlated to the degree of platelet reduction It has been proposed that the capillaries are unusually permeable or that they are incapable of adequate contraction For the latter hypothesis evidence has been presented which is based on direct observation

The *prolonged bleeding time* is explained by a failure of the capillaries to retract as well as by the lack of sufficient platelets to plug the opening of a bleeding vessel The intracutaneous oozing of blood when capillary pressure is increased (tourniquet test) is explained in the same way Coagulation time is normal because few platelets are needed to initiate clotting The clot however is loose and retracts poorly because a large number of platelets are needed for syneresis

Symptomatology Purpura hemorrhagica may begin abruptly and disappear spontaneously just as suddenly or its manifestations may seem to have been present a long time occasionally so long that they might appear to be characteristic of the individual concerned The bleeding may be mild with perhaps only inconspicuous purpuric spots in the skin or it may be severe and not only may lead to serious loss of blood but also may occur into vital areas such as the cranium or the diaphragm All variations between these extremes may be encountered and the disorder may wax and wane in intensity Acute and chronic forms of the disorder have been described and by some investigators are regarded as different entities It is not unusual for symptoms first to become apparent following an acute infection

The lesions in the skin usually consist of minute red hemorrhages which differ from telangiectases

symptoms is related to the quantity of methemoglobin present the rapidity with which the methemoglobinemia develops and the capacity of the individual's cardiorespiratory and hematopoietic systems to adjust to the hypoxia In general levels of less than 20 per cent methemoglobin are usually not associated with symptoms At levels of 20 to 50 per cent fatigue weakness dyspnea tachycardia headaches and dizziness may occur Only rarely is enough methemoglobin present to cause coma and death

Diagnosis Methemoglobinemia should be suspected in any patient with intense cyanosis especially if physical examination fails to reveal evidences of cardiovascular or pulmonary disease A detailed history of drug ingestion is helpful

To identify the abnormal pigment freshly drawn blood to which an anticoagulant has been added is centrifuged to determine if the pigment is extracellular or intracellular If the plasma is clear the whole blood may be shaken in air for 15 min If the blood remains dark intracellular pigments are present The blood should then be diluted 1 10 or 1 100 with water and examined in the hand spectroscope The absorption band of methemoglobin (630 mμ) may be confused with that of sulfhemoglobin (618 mμ) but on the addition of 2 or 3 drops of 5 per cent potassium cyanide the band due to methemoglobin disappears whereas the sulfhemoglobin band is unchanged The addition of hydrogen peroxide causes dissolution of the sulfhemoglobin band but not of the methemoglobin band

Treatment In patients with hereditary or congenital methemoglobinemia ascorbic acid a reducing agent may be given daily by mouth in an amount of 100 to 500 mg Methylene blue accelerates the normal cell reconversion mechanism and is effective in a daily dosage of 100 to 300 mg by mouth In patients with mild drug induced methemoglobinemia no therapy is necessary other than removal of the offending agent since reduction of the methemoglobin occurs rapidly as a result of the intact normal reconversion mechanism In those patients in whom therapy is necessary methylene blue 1 to 2 mg per kg body weight given intravenously over a 5 min period in a 1 per cent solution is the agent of choice If cyanosis has not disappeared within an hour a second dose of 2 mg per kg body weight should be given This drug may also be given orally in doses of 3 to 5 mg per kg body weight

SULFHEMOGLOBINEMIA

Sulfhemoglobin is a sulfur containing hemoglobin derivative The exact mode of linkage of the sulfur to the hemoglobin is unknown Sulfhemoglobin is not found in erythrocytes under normal circumstances Once it has been formed it is not reversible to hemoglobin the abnormal derivative *remaining in the erythrocytes until they are destroyed*

Sulfhemoglobinemia may result when one of the oxidizing drugs listed in Table 104 has been taken

Phenacetin (A P C Empirin Compound Anacin *Stanback) and acetanilid (Bromoseltzer) are* the drugs found most frequently to be the causative agents Constipation is present in at least half the patients and it has been suggested without documentary proof that this contributes to the development of the condition by enhancing the production of hydrogen sulfide in the bowel

Sulfhemoglobin is inert as an oxygen carrier and when it is present intense cyanosis results Somewhat less than 0 5 Gm sulfhemoglobin per 100 ml blood causes a degree of cyanosis equal to that of 1 5 Gm methemoglobin or 5 Gm reduced hemoglobin Although the concentration of sulfhemoglobin may be found to be as high as 10 Gm per 100 ml the life of the patient is not endangered and symptoms which can be attributed to the sulfhemoglobinemia are rarely present Since many of the patients in whom sulfhemoglobinemia develops are neurotic or are taking drugs for a chronic headache or constipation the symptoms which can be elicited are probably not attributable to the sulfhemoglobinemia Symptoms of bromide intoxication frequently complicate the clinical picture in those ingesting Bromoseltzer Once formed there is no way of removing the sulfhemoglobin except by phlebotomy In time the affected red corpuscles wear out and are destroyed Treatment requires interdiction of the offending drug and correction of the intestinal conditions causing the disorder

Enterogenous sulfhemoglobinemia is a term used to refer to the syndrome of sulfhemoglobinemia cyanosis and constipation or other evidence of disturbed bowel function without the history of the ingestion of an oxidizing or sulfur containing drug Rare cases of acquired hemolytic anemia with paroxysmal sulfhemoglobinemia and methemoglobinemia *have been reported*

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kopenia suggests leukemia aplastic anemia disseminated lupus erythematosus or one of the splenic disorders

Treatment and Prognosis The first principles in the therapy of thrombocytopenic purpura are expectant management and a search for possible etiologic factors If one is found or suspected further exposure should be stopped Expectant therapy in addition to appropriate rest nursing and diet includes iron if there has been blood loss and blood transfusion if this loss has been severe The use of siliconized apparatus or plastic equipment in transfusion or the use of platelet rich bloods or both is helpful as a temporary measure but it is noteworthy that platelet transfusions have limited value since platelet survival tends to decrease progressively when repeated transfusions are given

These measures are recommended because spontaneous remissions are common especially in children They can be complete and permanent Remissions are particularly likely to occur if the onset has been acute and there is no history of previous hemorrhagic manifestations Unfortunately the danger of bleeding into a vital organ such as the brain makes the waiting period a trying one Recurrences are twice as common in females as in males A more or less chronic course punctuated perhaps by more acute phases is more often seen in adolescents and adults but occurs at all ages

The use of adrenocorticotropic hormone cortisone or prednisone is often associated with a decrease of bleeding phenomena and the thrombocytopenia may decrease or disappear but these effects are temporary These hormones are useful chiefly therefore in the management of hemorrhagic emergencies and in the preoperative preparation of patients for splenectomy Those which can be given orally are preferred In general 75 to 250 mg cortisone or 20 to 60 mg prednisone is given per day in divided doses

Splenectomy results in "cure" in approximately two-thirds of patients Following splenectomy the platelet count may increase rapidly and to abnormally high levels an effect which carries the danger of postoperative thrombosis or it may rise gradually Bleeding often ceases even though the platelet count may not have increased greatly an effect which suggests an influence of the spleen on capillary function In the bone marrow the previously abnormal megakaryocytes in most instances soon appear to be quite normal again and are seen to be surrounded by platelets Even when splenectomy is not followed by complete recovery considerable improvement can be expected It is of interest that remission following splenectomy is not necessarily accompanied by disappearance of the "thrombocytopenic factor"

Benefit is less likely to follow splenectomy in acute phases of bleeding than in the more chronic phases and the operative mortality is higher hence hasty resort to operation should be avoided and the patient should be prepared as described already

In these patients other operations should not be carried out before splenectomy has been done since the bleeding may be severe and serious

NONTHROMBOCYTOPENIC PURPURAS

There are a number of types of purpura which are not accompanied by thrombocytopenia In none of these disorders has an abnormality of the blood been recognized In all but one a very rare syndrome known as von Willebrand s disease bleeding time is also normal These purpuras have been discussed already (p 215) but allergic purpura and certain other rare purpuric disorders deserve more complete consideration

Allergic Purpura

In this form of purpura there is found one or more of the common symptoms of allergy such as erythema, urticaria or effusions of serum into subcutaneous or submucous tissues or viscera There may be concomitant articular symptoms (*Schonlein s purpura peliosis rheumatica*) crises of abdominal pain (*Henoch s purpura*) or no localized signs (*purpura simplex*) Constitutional symptoms such as fever and malaise may be present The manifestations may wax and wane in intensity extent and nature In various combinations erythema (multiforme bullosum, vesiculosum nodosum) urticaria and edema may be encountered Necrotic areas may develop to be followed by the formation of bullae or ulcers The skin lesions may appear in crops and may be accompanied by itching or paresthesias There may be hemorrhage from the visible mucous membranes Kidney lesions similar in nature to those found in the skin may develop and cause hematuria proteinuria, and profound though temporary disturbance of renal function

Etiology and Pathogenesis These purpuras are more common in children and young adults than in older age groups The true nature of these purpuras is unknown The resemblance to serum sickness suggests an allergic basis but only in a minority has an allergic cause been demonstrated In some cases the exciting agent appears to have been bacterial (streptococcus antityphoid vaccine) or an article of food (milk eggs pork strawberries etc) In others hypersensitivity to cold has appeared to be the factor Comparison of the sex ratio age of onset seasonal trends and incidence of previous upper respiratory tract infections particularly those associated with a hemolytic streptococcus and similarities in the latent period before

Table 105 CLASSIFICATION OF THROMBOCYTOPENIC PURPURAS

I Essential or primary purpura hemorrhagica idiopathic thrombocytopenic purpura (ITP)
II Symptomatic purpuras
  A Chemical vegetable animal and physical agents
    1 Chemical
      a Myelosuppressive agents nitrogen mustards TEM Myleran urethan antimetabolites benzol
      b Agents which in therapeutic doses produce purpura mainly because of individual sensitivity organic arsenicals Sedormid quinidine quinine sulfonamide gold salts and possibly other agents (oxytetracycline phenylbutazone Tridione dinitrophenol organic hair dyes estrogens DDT)
    2 Vegetable Foods orris root
    3 Animal Snake venoms pertussis vaccine insect bite
    4 Physical X rays and other forms of ionizing radiation heat stroke extensive burns
  B Blood disorders
    1 Leukemias Acute or late stages of chronic
    2 Anemias
      a Aplastic—idiopathic or due to physical or chemical agents
      b *Myelophthisic (tumors in bone marrow osteosclerosis etc)*
      c Pernicious anemia
      d Acquired hemolytic anemias of immune body type
    3 Splenic disorders Congestive splenomegaly Gaucher s disease Felty s syndrome rarely Hodgkin s disease
    4 Miscellaneous Acute purpura with platelet thrombi in capillaries (thrombotic thrombocytopenic purpura)
  C Infections and other conditions Septicemia subacute bacterial endocarditis typhus measles vaccinia infectious mononucleosis etc lupus erythematosus sarcoidosis hemangioendothelioma massive blood transfusions

SOURCE Adapted from M M Wintrobe Clinical Hematology 4th ed Philadelphia Lea & Febiger 1956

in that they do not blanch on pressure Often ecchymoses are found as well Mucous membrane hemorrhages are common bleeding from the nose mouth or uterus being particularly frequent and sometimes severe Not rare are instances in which menorrhagia is the chief complaint and this often is the only prominent clinical sign other than the abnormalities in the blood Bleeding however may occur into any tissue and from any orifice Frequently also excessive bleeding may be noted following tooth extraction tonsillectomy operations or injuries

Fever of mild degree may be present in acute cases *The spleen may extend a fingerbreadth below* the costal margin There is no general glandular enlargement sternal tenderness or other physical sign other than those attributable to hemorrhage or anemia

Blood and Bone Marrow Findings These have in the main been mentioned already What platelets may be seen in the blood smear are often unusual in appearance giant or minute forms or deeply stained ones The bleeding time may be slightly moderately or greatly prolonged (8 to 60 min or *more)* Anemia *if present* is proportional to the amount of blood lost If there has been much bleeding signs of stimulated erythropoiesis will be found reticulocytosis polychromatophilia even occasional normoblasts The leukocyte count may be normal but if acute blood loss has taken place there may be a moderate leukocytosis with slight shift to the left In some chronic cases lymphocytosis has been observed

Diagnosis Hemorrhage not due to obvious cause if associated with thrombocytopenia prolonged bleeding time poor clot retraction and positive tourniquet test can be attributed to thrombocytopenic purpura Prolonged bleeding time is characteristic of von Willebrand s disease (p 1204) and may be found though rarely in a number of conditions in which coagulation time is prolonged provided the blood and tissues are severely impoverished in coagulation factors (see Table 20 *Chap 23 p 221) These include hemophilia and* hypoprothrombinemia A positive tourniquet test is found in many circumstances other than thrombocytopenic purpura (p 221) Poor retraction of the clot is found with rare exceptions only when the platelets are reduced in number The combination of these abnormalities is characteristic of thrombocytopenic purpura

Before a diagnosis of purpura hemorrhagica can be made however the recognized causes of thrombocytopenic purpura must be excluded They are listed in Table 105 The history and physical examination will serve to rule out many of these conditions Adenopathy and sternal tenderness as well as anemia out of proportion to the blood loss even in the absence of striking changes in the leukocytes should suggest leukemia Persistent leu

the clotting defect is similar to that in true hemophilia but which cannot be so regarded for various reasons

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216 HEMOPHILIA AND RELATED DISORDERS

M M Wintrobe

HEMOPHILIA

Definition Hemophilia is a constitutional anomaly of blood coagulation which depends on the inheritance of a sex linked recessive mendelian trait transmitted by the female and affecting only males It is characterized by a lifelong tendency to excessive bleeding The coagulation time is prolonged

History Although a clear description of this disorder was not published until 1803 by Otto of Philadelphia it is apparent from passages in the Talmud that the condition was known to the ancient Jews who even proscribed circumcision in those whose family history suggested this disorder

Etiology and Pathogenesis The factor or gene responsible for the development of hemophilia appears to be carried in the X chromosome of the reproductive cells The disease is limited to the male and is transmitted from the male through an unaffected daughter to a grandson The daughters of an affected male transmit the trait as an evident defect to half their sons and as a hidden (recessive) characteristic to half their daughters The occurrence of hemophilia in the female would require the marriage of a hemophiliac male with a carrier female Such cases have been described but they are exceedingly rare Sporadic cases of hemophilia have been described in which the family history was negative These can sometimes be explained by long inheritance through females with the males being by chance unaffected Illegitimacy may be responsible for other instances while still others may represent the disease arising *de novo*

It has now been shown that the abnormality in hemophilia is due to the absence or reduction in the blood of a component essential for the formation of plasma thromboplastin ("thromboplastinogen" antihemophilic globulin) The role which this substance plays in the process of coagulation was discussed earlier (Chap 23)

Symptomatology Hemorrhage usually following trauma but sometimes spontaneous is the essential symptom The bleeding is in the nature of a persistent slow oozing which is out of all proportion to the extent of the injury This tendency to prolonged bleeding usually appears in early childhood even in infancy The bleeding may last not only hours but days and even weeks and may lead to profound anemia Subcutaneous and intramuscular hemorrhages are common Petechiae are very rare Hematomas may be large There may be severe bleeding from the mouth gums lips tongue or gastrointestinal tract Epistaxis is a common symptom The eruption and loss of teeth may be accompanied by severe bleeding Hematuria is relatively common and hemorrhage into joints is characteristic Recurrences are the rule and ultimately a permanently swollen joint with local deformity contractures and muscular atrophy is produced

The *blood* in typical cases is normal except for the prolonged coagulation time and the manifestations which hemorrhage produces (p 1171) Cur

the onset of symptoms suggest a close relationship between the Henoch Schonlein syndrome and acute nephritis

It is likely that an antigen antibody reaction occurs which takes place especially in the endothelium of certain blood vessels As a result there is an alteration in the permeability of the small blood vessels Perivascular inflammation has been observed about the small vessels of the corium of the skin The various manifestations arise from extravasations of varying proportions of plasma and formed elements of the blood Mechanical factors may possibly influence the localization of the lesions in addition to the local vascular changes In Henoch s purpura an urticarial serohemorrhagic effusion into the intestinal wall is the cause of the colicky pain and sometimes even leads to intussusception

Diagnosis Diagnosis is most difficult when purpura is not present or not obvious In Henoch s purpura crises of pain may develop which in the absence of purpura and accompanied as they may be by leukocytosis cannot be clearly distinguished from acute abdominal conditions which call for operative intervention Eosinophilia may be present and then an allergic rather than an inflammatory reaction may be suspected Acute nephritis may be simulated when the kidney is involved Hematuria may be a prominent symptom in such cases just as melena may occur in Henoch s purpura The Schonlein type may be mistaken for rheumatic fever

When purpura is discovered and there are exudative skin lesions at the same time diagnosis is much easier since these lesions are not encountered in other forms of purpura as a rule Various chemical agents (e g quinine) may also produce non thrombocytopenic purpura Furthermore this may be a symptom of a variety of diseases already discussed (p 215)

Treatment and Prognosis Treatment is purely symptomatic Naturally if an etiologic agent is discovered or suspected further exposure should be eliminated Desensitization may be attempted if the exciting agent is protein in nature Allergic purpura is rarely fatal Individual attacks last from 1 to 6 weeks Recurrences at intervals of months or years are not unusual however and in some cases glomerulonephritis has developed in association with or in the wake of the purpuric disorder with the consequences usual in that condition Hormone therapy (ACTH cortisone) has been found to produce symptomatic benefit

Other Hemorrhagic (Purpuric) Disorders

A variety of hemorrhagic disorders characterized in the main by spontaneous bleeding from the mucous membranes and from the internal surfaces of the body and often by petechiae and ecchymoses as well have been described which cannot be fitted into the categories already discussed Posttraumatic and postoperative bleeding is not unusual in these cases Of these conditions *one von Willebrand s* disease is becoming better defined as an entity another Glanzmann s thrombasthenia is less clearly delineated

Von Willebrand's disease a hemorrhagic diathesis inherited as a simple mendelian dominant and affecting both sexes is characterized by prolonged bleeding time normal platelet count normal coagulation time and normal clot retraction The tourniquet test may or may not be positive The tendency to bleed appears early in childhood and takes the form of epistaxis bleeding from the gums or from the female genitalia Hemorrhage from the gastrointestinal or urinary tract may occur and there may be prolonged bleeding from injuries and operation sites The underlying defect in von Willebrand s disease may be an inherited abnormality of the capillaries of the skin and mucous membranes They have been described as distorted and often bizarre in form and fail to contract after injury

Under the title of *vascular hemophilia* several families have been described in which the characteristic features of von Willebrand s disease were associated with deficiency of antihemophilic globulin Inheritance of this disorder appears to be that of a non sex linked autosomal dominant with high penetrance and variable expressivity

Glanzmann s thrombasthenia is a term which has been applied to cases of excessive hemorrhage in which the bleeding time platelet count and coagulation time were normal but clot retraction was deficient and the platelet morphology abnormal This is the foundation of the concept of *thrombocytopathic purpura* in which it is assumed that bleeding occurs because of a *qualitative* rather than a quantitative platelet defect It is possible that several varieties of thrombocytopathic purpura depending on disturbances in any one of the several platelet functions may become better defined in time Thus in the so called *Glanzmann Naegeli* type of thrombasthenia small round platelets have been described normal or increased in number but with impaired adhesiveness and agglutinability Although clot retraction is poor prothrombin consumption is normal and coagulation time is normal

Surgical procedures in cases such as these should be avoided Bleeding is managed by pressure the application of thrombin fibrin foam and blood transfusion when necessary

The term *pseudohemophilia* which von Willebrand applied to the condition he described is unsatisfactory and if it must be used at all is more *appropriately applied to cases of abnormal bleeding* associated with prolonged coagulation time in which

ing proportions to normal blood The clotting of normal blood is not delayed by the addition of even 50 per cent of hemophilic blood

The one stage prothrombin time separates hemophilia from conditions associated with true prothrombin factor V and factor VII deficiencies and also from many cases in which there is a circulating anticoagulant In hemophilia in contrast to these conditions prothrombin time is normal The deficiency in hemophilic blood can be corrected by the addition of a small proportion of normal plasma The degree of reduction in antihemophilic globulin content can be assayed roughly by this means

It was pointed out earlier that assays for antihemophilic globulin have revealed a *mild* form of *hemophilia* in which even prothrombin consumption is normal or equivocal An additional observation of interest is the fact that unlike classic hemophilia some of the heterozygotes show a diminution in antihemophilic globulin a finding which suggests that the gene is not completely recessive as it is in classical hemophilia and for this reason the condition has been attributed to an allelic mutant of the hemophilia gene In female carriers of classic hemophilia no evidences of a coagulation defect have been demonstrated thus far and no deficiency of antihemophilic globulin has been found

Another entity clinically indistinguishable from classic hemophilia is referred to as *plasma thromboplastin component (PTC) deficiency* and *Christmas disease* The condition is due to the lack or deficiency of a coagulation factor necessary for the formation of thromboplastin which is present in normal and in hemophilic plasma Both severe and mild forms of the disorder have been encountered The coagulation time is usually prolonged and prothrombin consumption is impaired but cases with normal values have also been observed The missing coagulation factor is most readily obtained from serum Since this condition resembles hemophilia in its clinical manifestations and mode of inheritance it has been called *hemophilia B* the letter *A* being used to refer to the classic condition The two types of hemophilia can be distinguished in vitro by the correction of the coagulation defect of the one by the other and of both by the addition of normal plasma Another simple test consists in the correction of the clotting defect in PTC deficiency by the addition of normal serum and the failure of such correction in classical hemophilia

Still other disorders resembling hemophilia have been described They include *plasma thromboplastin antecedent (PTA) deficiency* which differs from hemophilia and PTC deficiency in that the manifestations occur in *either sex* The condition appears to be transmitted as an autosomal dominant trait with a high degree of penetrance but variable expression Spontaneous bleeding is rare bleeding has occurred usually following trauma or a surgical procedure including tooth extraction Various degrees of severity have been observed ranging from a severe form with prolonged coagulation time and markedly abnormal prothrombin consumption, to a mild form with normal coagulation time and only slightly impaired prothrombin consumption Thromboplastin generation is markedly impaired The deficiency in this disorder is corrected both by plasma absorbed with $BaSO_4$ which corrects AHG deficiency and by serum which corrects PTC deficiency PTA is a globulin which is stable on storage and is present in normal serum where it is localized in the β_2 globulin fraction Studies of the relative incidence of hemophilia PTC and PTA deficiencies have yielded ratios of approximately 15 2 1

A possible *fourth plasma thromboplastin component* (PTF D) has been described as the deficiency underlying the occurrence of frequent and severe epistaxes and imperfect hemostasis after tooth extraction or serious trauma In the reported cases coagulation time was prolonged prothrombin consumption was reduced and thromboplastin generation retarded The deficient factor has been characterized as heat labile and storage stable and as being present in both normal plasma and serum The blood of patients with PTA and that of patients with "fourth component deficiency have been found to be mutually corrective

Some investigators doubt the existence of the fourth component while some have reported cases in which still other factors (e g Hageman factor) were thought to be deficient

Course and Prognosis The tendency to bleed varies from time to time and differs in degree from one family to another The typical hemophiliac patient rarely survives to adulthood without suffering some disabling deformity of the joints The prognosis differs however in accordance with the severity of the AHG deficiency Death may occur from exsanguination following surgical procedures or accidental cuts Less often it is due to internal hemorrhage

Treatment The prevention of hemophilia depends on appropriate restriction of marriage or at least of propagation Only unaffected males can marry with any assurance that the hemorrhagic tendency will not be transmitted

Affected individual and male children of tainted stock must be guarded against trauma and surgical measures even the most minor ones should be avoided whenever possible If some procedure which may entail bleeding is absolutely necessary

Table 106 BLEEDING AND COAGULATION TESTS IN VARIOUS HEMORRHAGIC DISORDERS

Disease or condition	Thrombocytopenia	Bleeding time prolonged	Clot retraction poor	Tourniquet test positive	Coagulation time prolonged	Prothrombin time (one-stage) prolonged	Prothrombin consumption impaired
Purpura thrombocytopenic	+	+	+	+	−	−	+
Purpura nonthrombocytopenic	−	−	−	±	−	−	−
Hemophilia (hemophilia A)	−	−*	−	−	+†	−	+†
PTC deficiency (hemophilia B)	−	−	−	−	+†	−	+†
Dicoumarin excess	−	−	−	−*	−*	+	−
Factor V deficiency	−	−	−	−	+†	+	+
Factor VII deficiency	−	−	−	−	+†	+	−
Hypoprothrombinemia	−	−	−	−	+	+	−
Afibrinogenemia	−	+†	−	−	+	+	−
Anticoagulant excess	−	−*	−	−	+	±	±
von Willebrand's disease	−	+	−	±	−	−	−

* May be prolonged if condition is severe
† May be normal if condition is mild

ously the degree of prolongation of coagulation time like the symptoms of this disorder varies from time to time Platelets are normal in number Only *rarely is bleeding time prolonged*

It has been shown that cases of hemophilia occur which are less severe than the classic type just described Assays of plasma antihemophilic globulin (AHG) have shown a great range in the quantity of this essential substance Four grades of hemophilia have been distinguished viz classical hemophilia in which the plasma AHG is 0 per cent moderate hemophilia characterized by the occurrence of subcutaneous hematomas and post operative hemorrhages essentially normal coagulation time normal prothrombin consumption and less than 3 per cent AHG mild hemophilia in which coagulation time and prothrombin consumption are normal and the plasma AHG is approximately 16 per cent and subhemophilia in which there may only be a history of prolonged postoperative oozing The plasma AHG is in the neighborhood of 33 per cent as compared with the normal value of 65 to 136 per cent Frequently the severity of the disorder is constant in a given family as if not only the defect but also its degree were an inherited characteristic

The *bone marrow* is normal except for normoblastic hyperplasia when hemorrhage has been severe

Diagnosis Although hemophilia and purpura hemorrhagica are often confused with each other differentiation is easy as a rule for the latter condition involves thrombocytopenia prolonged bleeding time poor clot retraction and a positive tourniquet test In hemophilia the patient is normal in *these respects and in the classical disorder coagulation time is prolonged* There is in addition the history of repeated protracted hemorrhage usually first manifested in early childhood as well as the characteristic family history Occasionally difficulty in diagnosis may arise if attention is attracted only to the joint manifestations or to a swelling not recognized as a hematoma In a similar manner the bleeding may suggest kidney disease pulmonary disease or peptic ulcer

Other Disorders of Coagulation The development of more precise methods of laboratory examination has resulted in the discovery of new entities hitherto confused with classic hemophilia and the purpuras in addition to recognition of the fact that mild forms of hemophilia exist Many of these disorders were mentioned earlier (Chap 23) The results of various laboratory tests in a number of these conditions are presented in Table 106

In cases of hemophilia with normal or only slightly impaired coagulation time the prothrombin *consumption test will be found reliable and* sensitive although it is not specific reduced prothrombin consumption is found also in various disorders associated with thrombocytopenia as well as in patients with hemorrhagic manifestations due to anticoagulants affecting thromboplastic activity The absence of a circulating anticoagulant can be demonstrated by adding the patient s blood in vary

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M M Wintrobe

AGRANULOCYTOSIS

Definition Agranulocytosis (agranulocytic angina) is a disorder characterized by severe sore throat marked prostration and extreme reduction or even complete disappearance of the granulocytes from the blood This clinical picture first recognized by Schultz in 1922 was observed most frequently in women of middle age and often ended in sepsis and death An etiologic relationship to the taking of certain drugs has been demonstrated

Etiology and Pathogenesis In 1931 Kracke pointed out that the sudden appearance of this syndrome corresponded with the introduction of certain coal tar derivatives as therapeutic agents This was borne out by considerable circumstantial evidence which incriminated in particular the antipyretic aminopyrine (Pyramidon) The course of events in affected individuals would seem to be (1) granulocytopenia as the result of some effect induced by the drug (2) loss of resistance to infection development of sore throat (3) overwhelming sepsis and death That some form of tissue injury in addition to leukopenia may be a factor in the pathogenesis of this syndrome is suggested by the frequency with which one may encounter leukopenia even of severe degree following nitrogen mustard therapy without sepsis developing

The most striking change observed in the bone marrow is a lack of juvenile and segmented neutrophilic leukocytes less mature forms being plentiful This picture has been referred to as maturation arrest but it could as readily result from abnormal peripheral destruction of the leukocytes or their segregation somewhere

Drugs producing leukopenia may be divided into two main groups—namely those which produce this effect in all individuals if given in sufficient amounts and those which cause leukopenia only in certain sensitive persons (Table 107) Various data suggest that between 0 5 and 4 per cent of patients taking the second group of drugs develop granulocytopenia In group III are listed drugs which have been incriminated in a few case reports but they cannot be regarded as well established causes of leukopenia

It is likely that granulocytopenia develops by more than one mechanism Some cases are encountered in which no drug seems to be incriminated Those drugs which produce granulocytopenia in all persons when given in sufficient amounts probably do so through their toxic effects Agents such as aminopyrine probably require a peculiar sensitivity or idiosyncrasy on the part of the patient

Table 107 LEUKOPENIA PRODUCING DRUGS

Group I—regularly produce leukopenia if given in sufficient amounts
- Benzene
- Mustards (sulfur and nitrogen mustards TEM etc)
- Urethan Myleran Demecolcin
- Antimetabolites (antifolic acid compound 6-mercaptopurine etc)

Group II—produce leukopenia in "sensitive" persons only
- Analgesics (aminopyrine phenylbutazone etc)
- Antithyroid drugs (thiouracil methimazole etc)
- Anticonvulsants (trimethadione phethenylate etc)
- Sulfonamides [sulfanilamide sulfisoxazole (Gantrisin)]
- Antihistamines (Pyribenzamine phenothiazine etc)
- Antimicrobial agents (organic arsenical chloramphenicol)
- Miscellaneous (dinitrophenol chlorpromazine gold salts etc)

Group III—very rarely cause leukopenia if at all
- Barbiturates (acetanilid acetophenetidin)
- Quinine
- Cinchophen etc

Rarely other manifestations of sensitivity such as rash urticaria and edema may be present or may have occurred on other occasions Furthermore in patients who have recovered from aminopyrine induced agranulocytosis the administration of small amounts (0 2 Gm) of the drug may be followed within 6 to 10 hr by disappearance of all the neutrophils from the blood It has also been shown that the blood of such a person withdrawn 3 hr following ingestion of the drug produces outspoken granulocytopenia within 20 to 40 min after its transfusion into normal persons In the plasma and serum of the sensitive patient a substance has been found at the height of the aminopyrine granulocytopenia which produces agglutination of homologous and heterologous leukocytes If as seems likely an immune mechanism is involved in the pathogenesis of this type of granulocytopenia removal of the agglutinated leukocytes from the circulating blood may be postulated with resulting depletion of the more mature forms from the bone marrow

Symptomatology The condition described by Schultz was an *acute fulminating disorder* In such cases there may be a prodromal period marked only by malaise or moderate fever which often is overlooked If the granulocytopenia is recognized at this stage and sepsis is prevented or does not develop no other manifestations may appear If infection supervenes or if the condition is first recognized at this stage the onset appears to be sudden and is marked by a chill high fever and often sore throat *Prostration is extreme* Gangrenous ulceration may be found on the gums tonsils soft palate lips pharynx or buccal mucous membranes Regional

it should be done only in a hospital and when plentiful amounts of fresh blood and plasma or antihemophilic globulin are available Normal plasma kept solid or dried lyophilically within a few hours of its withdrawal from the body will retain its antihemophilic effect almost indefinitely Although as little as 50 ml fresh plasma will maintain the coagulation time of a hemophiliac of moderate severity within normal limits for about 24 hr in practice it is wise to use much larger amounts When internal bleeding occurs transfusions of blood and plasma are the only measures of value and carry the minimum of risk Surgery is contraindicated Prior to any surgical measure such as tooth extraction at least 500 ml fresh plasma should be given In contrast to its effectiveness in PTC deficiency serum is devoid of activity in classic hemophilia

An essential in the local management of bleeding in hemophilia is the avoidance of tissue injury The existence of damaged or devitalized tissue merely prolongs the period of subsequent hemorrhage Thus for example in dental extraction gum margins should not be sewn together When there is free bleeding pressure must naturally be applied but it should be temporary and gentle and should be supplemented by the use of coagulants such as Russell's viper venom or thrombin ("hemostatic globulin") These measures may be followed by the application of absorbable hemostatic dressings such as human fibrin fibrin foam gelatin sponge or oxidized cellulose Following tooth extraction a previously made dental splint will keep the dressing in place with a minimum of movement

Unfortunately in some patients with hemophilia antibodies with an anticoagulant action have developed following transfusion or treatment with antihemophilic globulin This appears to be due to immunization against the latter substance

HEREDITARY HEMORRHAGIC TELANGIECTASIA

Definition This is a vascular anomaly characterized by multiple dilatations of capillaries and venules in the skin and mucous membranes The anomaly is transmitted as a simple dominant by both sexes

Etiology The telangiectases may be found in childhood but they increase in number as age advances Bleeding may not commence until adult life has been reached

Symptomatology Epistaxis is especially common but bleeding may come from telangiectases wherever they are the face tongue lips or gastrointestinal respiratory or genitourinary tracts Those on the skin are less likely to bleed than are telangiectases on mucous membranes The telangiectases range from pin point to about 3 mm in diameter are bright red or violaceous in color and characteristically blanch on pressure Sometimes they form nodular vascular tumors the size of a split pea such lesions resemble those of a very rare probably nonhereditary condition angiokeratoma corporis diffusum (Fabry) In elderly patients some of the lesions may become spiderlike resembling those associated with hepatic insufficiency Trivial trauma sustained by these abnormal relatively exposed vessels results in an unusual amount of bleeding The blood is normal except for the effects hemorrhage may have produced The tourniquet test is negative

Diagnosis This depends on recognition of the vascular anomalies which are easily overlooked Purpuric spots do not fade on pressure

In a number of cases of this disorder pulmonary arteriovenous fistula has been observed

Treatment The telangiectatic vessels are excessively fragile but oxidized cellulose (Oxycel) Gelfoam or similar hemostatic agents usually suffice to control an existing hemorrhage if they are applied carefully Although the primary bleeding site can be cauterized or destroyed by electrocoagulation satellite lesions soon form nearby Prophylaxis is unsatisfactory Many procedures have been tried including estrogen and androgen therapy with doubtful effect

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size and not at all in shape Bleeding time is usually moderately prolonged the clot retracts poorly and the tourniquet test is positive Coagulation time is normal

The onset of the disorder is insidious The symptoms may be those attributable to anemia or the effects of thrombocytopenia or of granulocytopenia may dominate the clinical picture There is striking often "waxy" pallor but weight loss is unusual There may be bleeding from the nose mouth vagina or elsewhere Hemorrhages may be found in the eye ground or skin Ulceration in the mouth and pharynx or other evidence of infection may be encountered There is no sternal tenderness splenomegaly or hepatomegaly and lymph node enlargement if present is found only in relation to local infection

This picture may follow exposure to a variety of *chemical and physical agents* As with the causes of granulocytopenia the agents associated with the occurrence of aplastic anemia may be divided into two groups viz (1) those which regularly produce marrow hypoplasia and aplasia if a sufficient dose is given and (2) those which are only occasionally associated with such a change and presumably depend on idiosyncrasy In the former category may be included ionizing radiation (roentgen rays radioactive phosphorus etc) the mustards (sulfur and nitrogen mustards TEM etc) urethan Myleran benzol and the antimetabolites (antifolic acid compounds 6 mercaptopurine etc) It will be noted that these agents have been or are used in the treatment of leukemia Hodgkin s disease and related disorders Excessive dosage will result in the production of marrow aplasia Benzene (benzol) is no longer used in the treatment of leukemia but it is employed in many industries (leather enamel rubber lacquer electroplating airplanes linoleum celluloid etc) and must thus be kept in mind when aplastic anemia is encountered in a person working in one of these industries Of the agents occasionally associated with the occurrence of hypoplasia or aplasia of the bone marrow the following should be mentioned in particular antimicrobial agents (arsenobenzols chloramphenicol) anticonvulsants (Mesantoin) antithyroid drugs antihistamines insecticides and various miscellaneous agents such as gold preparations and trinitrotoluene Although the evidence incriminating these drugs is only circumstantial a sufficient number of cases has been reported to make it seem very likely that development of aplastic anemia following exposure to the drugs named is more than a coincidence Less convincing is the evidence that other drugs are the cause of aplastic anemia since there are only single or very few reports incriminating them In this last group may be mentioned the sulfonamides oxytetracycline chlortetracycline Tridione Nuvarone Carbimazole Tapazole quinacrine phenylbutazone chlorpromazine and various hair dyes and volatile insecticides

"*Idiopathic* cases have also been described in which exposure to an offending agent could not be discovered Such cases have been observed most frequently in young adults or adolescents Still another form of pancytopenia with hypoplastic bone marrow has been observed usually at an even younger age which may be familial and is associated with a variety of congenital defects (bone abnormalities particularly of the forearms and thumbs microcephaly hypogenitalia genitourinary tract abnormalities) and a generalized olive brown pigmentation of the skin (*Fanconi syndrome*)

In addition to such cases of classic aplastic anemia a very similar clinical and hematologic picture can be observed in the face of a bone marrow picture which is cellular or even hyperplastic In still other cases little or no reduction was present in the leukocyte or platelet count Such *pure erythrocyte hypoplasia* has been observed as a congenital disorder but rarely it appears also to be acquired In some of these cases occasional nucleated red corpuscles polychromatophilia stippling and immature white cells have been found in the blood and splenic and hepatic enlargement and even general lymphadenopathy have been described Whether all these cases should be classed with the true aplastic anemias under one category of re fractory anemias" is a question which cannot be settled until their pathogenesis is clear That these various pictures may be variants of the same fundamental process is suggested by the observation that benzene poisoning not only may produce aplastic anemia but also can be associated with a regenerative blood picture including even a leukemoid reaction and the bone marrow may be hyperplastic rather than acellular Again *internal irradiation* produced by the ingestion of radium by watch dial workers was found to be characterized by *macrocytic* anemia with nucleated red corpuscles in the blood and bone marrow with primitive red corpuscle and leukocyte hyperplasia

Myelophthisic Anemia

This term is applied to the type of anemia associated with space occupying disorders of the bone marrow Metastatic carcinoma (for example that arising from malignancy of the breast prostate lung kidney adrenal or thyroid) leukemia multiple myeloma and a rare disorder known as *myelofibrosis* or myelosclerosis are conditions which produce *myelophthisic anemia* In *myelosclerosis* there is an irregular increase of fibrous or bony tissue in the bone marrow which is often associated with progressive anemia The outstanding symptom is splenomegaly The course is very slow Bone

adenopathy may be present but generalized adenopathy and sternal tenderness are not found and splenomegaly when present is minimal Brawny edema of the neck can become extreme Necrosis of the gastrointestinal tract may occur Jaundice has been described in some cases In fatal cases the duration of the illness is 3 to 9 days

In the blood granulocytopenia is the outstanding finding Since the leukocyte count is usually under 3 000 per cubic millimeter and often is as low as 500 a reduction in the absolute number of all cells actually takes place Of the leukocytes which remain 95 to 100 per cent may be lymphocytes Anemia and thrombocytopenia are not found If present another cause should be suspected

The *bone marrow* is normal except for the "maturation arrest described already

In addition to the acute form described above *chronic cyclic* and *recurrent* forms of granulocytopenia have been observed They may or may not be related to the acute disorder In the chronic cases the course is prolonged and infections which often are relatively resistant to therapy especially in the skin and oral cavity occur repeatedly Hypo*plasia of granulocytic precursors in the bone mar*row slight splenomegaly and absolute lymphocytosis and monocytosis have been described In other instances there is a cyclic or recurrent periodicity of attacks at intervals of weeks or months with more or less normal leukocyte counts in the symptom free period Unexplained fatigue is a common complaint In some cases the leukopenia has been observed to occur in remarkably regular 3 week cycles (*periodic neutropenia*)

Primary splenic neutropenia is a name applied to a clinical picture characterized by fever pain over the splenic region and splenic enlargement granulocytopenia and essentially normal or somewhat hyperplastic bone marrow The manifestations may be acute subacute or chronic and have been attributed to excessive lysis of neutrophils by the spleen Splenectomy is reported as bringing complete relief and excessive phagocytosis of leukocytes can then be demonstrated in that organ The disorder is very rare

Diagnosis The clinical picture may suggest a variety of buccal and pharyngeal infections The great majority of these infections however are accompanied by leukocytosis Infections characteristically accompanied by leukopenia such as measles undulant fever and typhoid should rarely give difficulty although influenza may Aleukemic leukemia may present a similar clinical picture but the presence of sternal tenderness general glandular enlargement and splenomegaly as well as anemia thrombocytopenia and usually very immature leukocyte in the blood makes differentiation no serious problem Aplastic anemia is recognized by evidence of involvement of red corpuscles and platelets as well as leukocytes

Treatment and Prognosis The offending drug must be searched for and its further use prohibited Of equal importance is the administration of chemotherapeutic agents such as penicillin which will hold the infection in abeyance until leukocyte formation becomes normal and is able to cope with the offending organisms There is no conclusive evidence that various agents which have been proposed as stimulants of leukocyte recovery including one which was at one time very popular Pent nucleotide are of any value Before the sulfonamides and penicillin were available the prognosis was very poor Mortality was as high as 70 to 90 per cent With modern chemotherapy only a small proportion of patients fail to recover During recovery with the reappearance of leukocytes abscesses may develop which will require appropriate therapy

Splenectomy has been associated with considerable improvement or even recovery in some cases of the recurrent and cyclic variety but this result is unpredictable The steroid hormones may be of temporary value perhaps in the cases most likely to respond to splenectomy In the chronic cases with hypoplastic bone marrow splenectomy has not been found to be helpful

THE PANCYTOPENIAS

Definition The term *pancytopenia* refers to a reduction in the number of all three formed elements of the blood the red corpuscles the leukocytes and the platelets This is not a disease entity but a triad which is encountered under a widely differing group of circumstances

Classification This triad may be encountered in aplastic or hypoplastic" anemia in "aleukemic or subleukemic leukemia in myelosclerosis and other myelophthisic anemias in pernicious anemia and in association with a number of disorders of the spleen Under this heading agnogenic myeloid metaplasia and primary splenic panhematopenia must also be considered

Aplastic Anemia

This term in its strict sense refers to a condition in which signs of hematopoiesis are lacking in the bone marrow fat having replaced the blood forming tissue At the same time there are anemia granulocytopenia and thrombocytopenia There are no signs of blood regeneration The reticulocyte count is very low or zero there is no polychromatophilia or basophilic stippling and nucleated red corpuscles and immature leukocytes of all types are absent The anemia is usually normocytic sometimes macrocytic the red corpuscles vary little in

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218 THE LEUKEMIAS
M M Wintrobe

Definition Leukemia is a disease probably of neoplastic nature which is characterized by widespread and abnormal proliferation of the leukocytes and their precursors throughout the body and particularly in the bone marrow spleen and lymph nodes There are different types of leukemia differentiated mainly according to the predominant abnormal cell forms The morbidity of the process ranges from a very acute disorder of but a few weeks duration to a very chronic one compatible with life even for many years The termination however is always fatal

History Knowledge of leukemia can be traced back to the period from 1839 to 1845 when Donne made the first microscopic observations and Craigie Bennett and Virchow distinguished the clinical entity Virchow recognized the cells as being leukocytes not pus cells and distinguished a lymphatic and a splenic type of leukemia With the development of Ehrlich s blood staining methods in 1891 Neumann s myelogenous form was recognized as being the same as Virchow s splenomegalic type Acute leukemia was recognized by von Friedreich in 1857 and by Ebstein in 1889 and the myeloblastic form was separated from the lymphoblastic type when Naegeli described the myeloblast in 1900 Reschad and Schilling Torgau described monocytic leukemia in 1913 Since then variations from the classic pictures have been recognized and method for palliative management have been developed but little advance has been made in gaining an understanding of the actual cause of this invariably fatal process or in its prevention or specific treatment

Varieties of Leukemia and Incidence of Various Types Acute and chronic forms of leukemia can be distinguished on clinical grounds as well as on the basis of the predominant abnormal cell types Without treatment acute leukemia usually is fatal within 6 *months* the duration of life in chronic leukemia may be several usually 3 to 5 sometimes 1 or 2 and in other cases 10 or more *years* "Subacute" leukemia is not truly intermediate between acute and chronic leukemia The course and the clinical and hematologic pictures resemble those of the acute form but the progress of the disease is slower than in the acute form of the disease Since myeloblasts lymphoblasts myelocytes lymphocytes or monocytes are the predominant cells in the great majority of cases of leukemia the terms *acute* or *chronic* (and if one wishes *subacute*) qualified by the name of the predominant cell type appear to be the most satisfactory designations for the different varieties of leukemia

Leukocytosis is found in the majority of cases of leukemia "Aleukemic or more correctly subleukemic leukemia refers to cases in which leukocytosis is absent Such cases are more often acute than chronic

Leukemia is as common a cause of death as diphtheria or measles Deaths from leukemia represent about 3 6 per cent of those due to cancer There has been a steady increase in the number of deaths from leukemia the number having tripled since 1930 Contrary to earlier statistics it appears now that the proportions of cases of chronic myelocytic and chronic lymphocytic leukemia are approximately equal Chronic leukemia is perhaps twice as common as the acute variety The incidence of the various types of acute leukemia including monocytic leukemia is difficult to determine because conclusions must be based on differences in interpretation In various series 11 to 21 per cent of the cases were subleukemic

Etiology and Pathogenesis While any variety of leukemia may occur at any *age* it is nevertheless true that acute leukemia is much more common before the age of twenty five than later and is especially frequent under five years of age chronic myelocytic leukemia has its highest incidence between the ages of twenty five and forty five and chronic lymphocytic leukemia is seen especially after the age of forty five or fifty A difference in the sex incidence of leukemia becomes perceptible as age advances there being essentially no difference in the occurrence of acute leukemia in male and female children and young adults a slight preponderance of chronic myelocytic leukemia in males and a distinct preponderance of chronic lymphocytic leukemia in males (3 1)

On the basis of past experience it can be stated that the probability that leukemia will occur *more*

marrow involvement may also occur in Hodgkin s disease and in the primary xanthomatoses (Gaucher s disease Niemann Pick disease Schuller Christian disease)

Agnogenic Myeloid Metaplasia

The term agnogenic myeloid metaplasia has been applied to cases in which the spleen showed marked myeloid metaplasia apparently as the result of a compensatory reaction This does not seem to be a disease entity The bone marrow has been variously fibrotic hyperplastic aplastic or normal The blood picture has varied like that described under Myelophthisic Anemia above In some cases jaundice was present In a number of instances a history of exposure to certain industrial solvents including benzene and carbon tetrachloride was obtained

Primary Splenic Panhematopenia

Primary splenic panhematopenia is the term which has been applied to cases associated with splenomegaly in which all three formed elements of the blood have been reduced in number and where excessive phagocytosis of these elements by the splenic macrophages has been conceived as being the fundamental disorder Splenectomy is described as producing dramatic improvement In these cases little or no evidence of increased blood destruction has been observed the reticulocyte percentage has been slightly or greatly increased polychromatophilia has been noted and the bone marrow picture has been one of hyperplasia As will be pointed out in the next section many splenic disorders are accompanied by pancytopenia

Diagnosis and Treatment It is evident from this outline that pancytopenia may be due to a number of causes of greatly varying nature The recognition of the underlying disorder will depend on thorough study which includes a painstaking history with careful inquiry about possible exposure to toxic agents thorough physical examination and bone *marrow examination in addition to a complete* survey of the blood

While the *blood picture* in these conditions may be that of a pancytopenia it is necessary to stress that *this is not* always the case Anemia is variable in degree It may be normocytic or macrocytic and nucleated red corpuscles may be seen in the blood even when there is little anemia Reticulocytes may be increased and polychromatophilia and stippling as well as teardrop poikilocytes may be present The leukocyte count may be normal reduced or increased If there is leukopenia there may be a uniform reduction in all the cells The blood may contain myelocytes and myeloblasts The platelet count may be normal or moderately reduced

However bone marrow punctures in various sites (sternum pelvic crest spinous processes) may be required before tumor cells are discovered Roentgenograms especially of the bones may be helpful and trephine biopsy of the marrow may be necessary If an enlarged lymph node is accessible it may be advisable to examine this microscopically and other procedures may need to be carried out in the search for malignancy A diagnosis of idiopathic aplastic anemia or of primary splenic panhematopenia" should be one of exclusion

Treatment will depend on the nature of the underlying disorder Blood transfusions are of temporary value in all the conditions which may produce this picture Ultimately if many transfusions are given hemochromatosis is produced since the iron from the transfused cells cannot be excreted Liver extract vitamin B_{12} folic acid and iron are of no value The temptation to remove an enlarged spleen must be tempered with good judgment This is especially important in those cases in which the spleen has assumed the function of the bone marrow for in such cases splenectomy can be harmful and at least is often of little or no value Nevertheless occasional patients derive definite benefit from splenectomy particularly when there is severe thrombocytopenia or increased blood destruction In cases in which large numbers of leukocytes in the circulating blood have been present roentgen therapy or chemotherapy such as that used in the treatment of chronic leukemia has been helpful

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Early in the disease the "shift to the left" is usually orderly with fewer metamyelocytes than segmented neutrophils fewer myelocytes than older forms and often few or no myeloblasts Later the myelocytes including the earlier forms tend to dominate the picture especially in the most advanced and more "acute" stages Eosinophils and basophilic leukocytes are likely to be found sometimes in substantial numbers If they are very numerous the terms *eosinophilic leukemia* and *basophilic leukemia* are appropriate The leukocyte count most often ranges between 100 000 and 500 000 cells per cubic millimeter when the disease is first discovered but values as great as 1 000 000 are sometimes seen Monocytes are present in normal or slightly increased numbers whereas lymphocytes though reduced in percentage maintain about a normal absolute value

The degree of anemia is a good index of the extent of the leukemic process In the earliest stages there is no anemia in far advanced cases it is profound The manner in which anemia is relieved when therapy reduces the extent of myeloid infiltration or becomes more severe as the disease advances gives support to the view that its cause is related to encroachment on the erythrocyte-forming elements by the leukemic cells The anemia is usually *normocytic in type* A few normoblasts are likely to be seen in the blood smear as well as slight polychromatophilia and occasional stippling

The platelets are normal in number or increased except in the terminal stages of the disease when *infiltration is very extensive* Then hemorrhagic manifestations prolonged bleeding time and other signs of secondary thrombocytopenic purpura are found In rare cases the platelet count may be extremely high and even megakaryocytes or fragments thereof may be found in the circulating blood

Chronic Lymphocytic Leukemia The onset is insidious as in the myelocytic form but the first symptom is likely to be painless enlargement of lymph nodes in the neck axilla or groin In other instances manifestations of anemia may dominate the picture and less commonly splenic enlargement or hemorrhagic manifestations may be the presenting complaints The skin is more often involved in the lymphocytic form than in the myelocytic as are also the gastrointestinal tract and the mediastinum There may be itching and burning with yellowish brown red bluish red or purple nodular skin lesions Bone tenderness is less frequent than in myelocytic leukemia The lymph nodes vary in size from that of a pea to that of a hen s egg and, though they are discrete several lying together may produce a huge mass They are moderately firm and smooth. Other manifestations are similar to those encountered in chronic myelocytic leukemia

The *blood picture* is that of a monotonous collection of small lymphocytes each looking just like its fellow contrasting strikingly with the colorful picture of myelocytic leukemia The leukocyte count more often ranges between 50 000 and 250 000 per cubic millimeter than at higher levels and 90 per cent or more of these cells are lymphocytes They often possess only a narrow rim of cytoplasm and may even appear to have none Larger lymphocytes may be seen but true "blast" forms with clearly defined nucleoli are unusual

As in myelocytic leukemia the presence or absence of anemia and its degree are good indexes of the extent of infiltration The anemia is normocytic and there may be occasional immature red cell forms in the blood smear Early the platelet count is normal as the disease advances it becomes greatly reduced and hemorrhagic manifestations may develop

Acute Leukemia The onset of acute leukemia is frequently rather abrupt and depending on the location and nature of the initial disturbance a great variety of clinical pictures may be encountered The initial symptoms may arise from leukemic infiltrations and glandular enlargement from hemorrhages or as the result of the systemic effects of the disease including those associated with anemia Sore throat abnormal bleeding from the mucous membranes or petechiae or ecchymoses in the skin cough or dyspnea resulting from enlargement of the thymus or mediastinal lymph nodes rheumatoid pains and a variety of neurologic complaints are among the manifestations which may be encountered Excessive bleeding following the extracting of a tooth or from minor injuries may be the first evidence of the disease Fever headache and general malaise may be soon followed by marked prostration and the onset of some severe malignantly virulent form of sepsis may be suspected

Lymph node enlargement is usually less conspicuous than in chronic leukemia but a systematic search will frequently reveal more or less generalized involvement of the lymph nodes The spleen is usually palpable but is rarely very large The liver is often enlarged The gums may be swollen and purplish in color and there may be ulceration in the mouth Sternal tenderness is present in the great majority of cases

The various types of acute leukemia cannot be differentiated on clinical grounds and this is often difficult even from the *blood examination* Anemia is practically always present when the disease is first discovered often it is severe The anemia is usually normocytic, *sometimes macrocytic* Poly

than once in a family is very small This seems strange when one considers the fact that suscepti bility to experimental leukemia and the transmission of the spontaneous disease in experimental animals follow definite genetic laws The explanation proba bly lies in the fact that although hereditary factors do exert an influence on the etiology of human leukemia as exemplified by familial cases of chronic lymphocytic leukemia especially their effect is modified by external influences and by other genes External factors include the effects of irradiation and perhaps also of trauma Leukemia has been described so much more often in persons exposed to radiation such as roentgenologists and those who were exposed to the atom bomb in Japan than in those not so exposed that this agent cannot be overlooked in a consideration of etiologic factors Not so well documented but nevertheless deserv ing serious consideration as *causes of leukemia* are trauma especially to bones and exposure to certain chemical agents especially benzol

The *cause* of leukemia is unknown The febrile character of acute leukemia and the evidences of infection about the mouth especially which can be seen in many cases have led some to hold the opinion that the disease is caused by an infectious agent Such a concept is difficult to accept in view of the fact that none of the other customary evi dences of infection have been observed such as transmission from man to man or from mother to fetus Experimental fowl leukemia it is true is carried by a filtrable agent but this is the case also with certain other types of neoplasms Newer knowledge is developing concerning the existence of transmissible cytoplasmic agents which deter mine the character of cells It is the more general view therefore that leukemia is neoplastic in char acter The transmission of experimental mammalian leukemia is generally thought to depend upon the transfer of viable cells In many cases of leukemia furthermore peculiarities can be observed in the leukemic cells which are like those of neoplastic cells including abnormal size and number of nucleoli and atypical as well as abnormal mitoses

Pathology The fundamental change in leukemia is widespread proliferation in the tissues and usu ally also in the blood stream of cells of a particular type In chronic myelocytic leukemia the bone mar row and spleen are chiefly involved but the lymph nodes liver kidneys lungs skin and other organs are also infiltrated The splenic pulp is full of myeloid cells and infarcts are commonly present In the chronic lymphocytic variety the lymphoid organs in particular show striking hyperplasia with disturbance of architecture and the liver bone marrow and other tissues are affected as well In acute leukemia the changes are similar and are ac companied by evidences of hemorrhage the result of the accompanying thrombocytopenia

CLINICAL MANIFESTATIONS

The clinical manifestations of the chronic and the acute leukemias differ from one another a great deal but there is comparatively little difference in the symptomatology of the various types of chronic leukemia and essentially no difference in the clini cal pictures of the different forms of acute leukemia

Chronic Myelocytic Leukemia The onset is in sidious and complaints may not develop until the disease has been in progress for a long time per haps a year or two The most common symptoms are those of anemia (weakness pallor palpitation or dyspnea) or a dragging sensation or swelling *in the left side of the abdomen due to the splenic* enlargement or complaints attributable to the in creased metabolic rate which develops as the disease progresses (loss of weight weakness nervousness cachexia etc) There may be slight fever rising as high as 101 F rarely higher As the disease advances the clinical picture may become more acute in that chills and fever may develop weight loss may become excessive and an abnormal tend ency to bleed may become manifest

The appearance of the patient ranges from that of seeming perfect health to one of extreme cachexia with marked pallor Splenomegaly is often the first physical sign of the disease The spleen may be just palpable or it may be huge the abdomen pro tuberant from this cause standing out in striking contrast to the general emaciation Lymph node enlargement is rarely significant but tenderness elicited on pressure over the lower portion of the sternum is a moderately early sign

Other symptoms and signs are less common but any system of the body can be affected The *liver* is often enlarged sometimes greatly and like the spleen is firm and not tender The *skin* may show small bluish gray elevated nodules due to specific infiltration The *retinas* may show hemorrhages and leukemic infiltrations There may be subperiosteal infiltration and even destructive lesions of *bone* leading to pathologic fractures Deafness from in filtration in the middle or inner ears or from hemor rhage evidences of nervous system involvement due to the same causes hematuria in association with infiltration of the kidney or other still less common manifestations may be observed Pain may develop from perisplenitis or in some cases pleural effusion may occur

The blood picture depends on the stage of the disease The earliest manifestation is leukocytosis due to an increase in the myeloid series of cells

similar to those seen in leukemia The term *erythroleukemia* refers to a very rare disorder in which there appears to be a combined neoplastic hyperplasia of both erythroblastic and leukoblastic tissues Cases such as these and lymphosarcoma cell leukemia plasma cell leukemia and cases of lymphocytic leukemia with only minor changes in the blood give support to the view now widely held that these conditions and those chiefly affecting lymph nodes such as lymphosarcoma as well as multiple myeloma are very closely related disorders or simply variations of a single abnormal process

DIAGNOSIS

The diagnosis of leukemia is not difficult in most cases Confusion may arise when the blood has not been examined thoroughly when the question of a leukemoid reaction arises or when the blood is subleukemic

Instances of chronic leukemia because of lymph node or splenic enlargement may suggest one of the various disorders affecting lymph nodes or the spleen (Chaps 219 and 220) or if the chief symptoms draw attention to other systems of the body a very great variety of conditions may be simulated Acute leukemia as already mentioned may suggest acute inflammatory conditions of various kinds purpura hemorrhagica or other disorders

Hematopoietic responses which suggest leukemia (*leukemoid pictures*) may be observed under a variety of circumstances

1 In association with *infections* A picture resembling myelogenous leukemia is sometimes associated with pneumococcal and meningococcal infections and rarely is seen in diphtheria and tuberculosis Lymphocytic leukemia may be suggested by the leukocytic reaction in whooping cough infectious mononucleosis and infectious lymphocytosis in particular and sometimes in chickenpox

2 *Intoxications* In rare instances of eclampsia severe burns diabetic acidosis and mercury poisoning leukemoid pictures have been observed

3 *Malignancy* especially with bone metastases as well as in multiple myeloma myelosclerosis and Hodgkin s disease

4 Following *severe hemorrhage or the rapid destruction of blood* when the profound stimulus to the bone marrow may bring forth a marked leukocytosis as well as immature forms of the nucleated red corpuscle series

The essential findings in the blood which favor leukemia rather than a leukemoid reaction are (1) pronounced immaturity of the leukocytes which is more significant than their number and (2) evidence of other hematopoietic disturbances which includes (*a*) anemia (*b*) the presence of immature red corpuscle forms in the blood such as nucleated red corpuscles and polychromatophilia and (*c*) platelet abnormalities especially thrombocytopenia Only in the early stages of chronic leukemia are anemia and other signs of disturbed hematopoiesis lacking In leukemia the immaturity of the leukocytes often is not orderly as in the case of a physiologic response where there are successively fewer numbers of the various immature forms with at most but a small number of myelocytes and but 1 or 2 per cent of myeloblasts

These criteria usually suffice to distinguish leukemia from a leukemoid reaction In addition the clinical findings such as splenomegaly lymphadenopathy and sternal tenderness make it apparent that one is dealing with leukemia On rare occasions however differentiation is quite difficult for the disease simulating leukemia may be accompanied by some of these physical signs and even immature forms of the red corpuscle series may find their way into the blood

In subleukemic leukemia especially and in the less clear instances where leukocytosis is present the *bone marrow* examination is very helpful for there abnormalities will usually be found which are well beyond the normal variations Only in the early stages of chronic lymphocytic leukemia or in the rare cases in which the marrow involvement is not diffuse is the sternal puncture likely to be disappointing In chronic myelocytic leukemia the cells in the bone marrow may be at a slightly less mature level than in the blood In acute myeloblastic leukemia even when there are few immature forms in the blood the marrow is crowded with myeloblasts In other types of acute leukemia the corresponding cells or their precursors will be found in large numbers in the marrow (see p 207)

Other examinations which may be helpful in reaching a diagnosis include *roentgenography* of the bones which may reveal subperiosteal infiltration osteolytic or tumorlike changes measurement of the *basal metabolic rate* which is increased in many cases of leukemia and sometimes lymph node biopsy

COURSE AND PROGNOSIS

With the possible exception of four instances there are no authentic reports of cure of leukemia In chronic leukemia the course is rarely interrupted by spontaneous remissions In acute leukemia such remissions are observed occasionally especially following infections and may last for several weeks The duration of life in cases of chronic leukemia varies greatly In some death ensues in a year or two after symptoms first appear in others the course may be extremely protracted extending over 10 or 15 years and very rarely even longer In certain cases such apparent long or short dura

chromatophilia as well as normoblasts is often found The platelet count is usually decreased at least to some degree even when the disease is first discovered The bleeding time then is prolonged the clot retracts poorly and the tourniquet test is positive

The leukocyte count rarely attains levels higher than 100 000 per cubic millimeter not infrequently it is below normal even below 1 000 At first glance the predominant cells are likely to be mistaken for lymphocytes Well stained thin smears are needed to demonstrate that the cells are abnormal and contain nucleoli When they are lymphoblasts or myeloblasts or even more immature forms (stem cells) they are difficult to distinguish from one another The nuclear differences are not easily recognized even by those with considerable experience and their cytoplasm is scanty and nongranular However in *acute myeloblastic leukemia* a small proportion of cells of slightly later development will often be found which will be seen to contain peroxidase positive granules Since such cells are lacking in *acute lymphoblastic leukemia* differentiation can sometimes be made on this basis *Acute monocytic leukemia* can be distinguished more easily however The pure and rarer form the *Schilling type* is characterized by the presence of large cells with lacy chromatin irregular nuclei inconspicuous nucleoli and irregular cell borders The cytoplasm contains innumerable very fine dustlike granules At the same time a few nongranular "blastlike" cells with nucleoli are found probably monoblasts In the *Naegeli type* of monocytic leukemia myelocytes are found in relatively large numbers in addition to cells resembling monocytes

Less Common Types of Leukemia *Subleukemic (Aleukemic) Leukemia* This term refers to those cases of leukemia of any type in which the leukocyte count is only slightly elevated normal or less than normal In such cases the abnormal cells may not predominate in the blood smear in fact they may be scarce and may not be readily discovered In most instances in which leukemic cells are stated to be absent however a good smear and stain and careful scrutiny by a person with some experience will usually reveal at least a few In any event the bone marrow contains a large number of the abnormal cells although sometimes they may be held together so firmly that they are not readily aspirated A normal or subnormal leukocyte count may be encountered at some stage of chronic or acute leukemia especially the latter This may be followed by a phase of leukocytosis or more often leukocytosis may be only a terminal event Sometimes leukocytosis never develops

Chloroma This term refers to a variant of acute leukemia which is characterized by the presence of greenish localized tumors connected particularly with the periosteum and ligamentous structures of the skull paranasal sinuses orbits spine ribs and sacrum Protrusion of an eyeball with diplopia and loss of vision pain deafness and signs of various cranial nerve palsies or other effects of pressure or infiltrative growth in a case otherwise consistent with a diagnosis of acute myeloblastic leukemia should lead to suspicion of chloroma

Chronic Monocytic Leukemia The great majority of cases of monocytic leukemia are acute or subacute as already described A small number are slower in their course Relatively low or subnormal leukocyte counts bone pain and cutaneous manifestations have characterized these cases

Lymphosarcoma Cell Leukemia The "lymphosarcoma cell" is about 9 to 14 μ in diameter has a sparse but deeply basophilic cytoplasm an oval oblong or kidney shaped nucleus with coarsely reticular spongy chromatin and a single prominent nucleolus Such cells are seen in cases fitting the category of "leukosarcoma" proposed by Sternberg Enlargement of lymph nodes in any one of many sites but especially in the anterior mediastinum or symptoms referable to anemia may for months or even years precede the appearance of these cells in the blood The leukocyte count may remain normal or low for a long time or even throughout the illness even though 30 to 98 per cent of the cells may ultimately be of the lymphosarcoma cell type

Plasma Cell Leukemia This term is applied to rare cases in which plasma cells have been found in the blood but which in other respects resemble leukemia—i e there is leukocytosis anemia and splenic and frequently lymph node and hepatic enlargement This disorder is perhaps but a variant of plasma cell myeloma but in contrast to typical multiple myeloma (Chap 221) bone involvement and hyperproteinemia may not be present There may be extraosseous plasmacytomas in the upper respiratory passages the cornea the pleura and elsewhere

A number of other still more rare forms of leukemia have been described They include so called megakaryocytic and acute megakaryoblastic leukemia eosinophilic leukemia and basophilic or mast cell leukemia The clinical course of some cases of eosinophilic leukemia is so unlike that of myelocytic leukemia that in some instances one wonders whether they represent true leukemia *Acute and chronic erythremic myelosis* refers to a disorder in which the erythropoietic tissue rather than the leukopoietic tissue seems to be involved in a neoplastic process The blood contains numerous erythroblasts in all stages of maturation but the most immature forms are found in disproportionately large numbers Other manifestations are

similar to those seen in leukemia The term *erythroleukemia* refers to a very rare disorder in which there appears to be a combined neoplastic hyperplasia of both erythroblastic and leukoblastic tissues Cases such as these and lymphosarcoma cell leukemia plasma cell leukemia and cases of lymphocytic leukemia with only minor changes in the blood give support to the view now widely held that these conditions and those chiefly affecting lymph nodes such as lymphosarcoma as well as multiple myeloma are very closely related disorders or simply variations of a single abnormal process

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tion depends respectively upon early diagnosis or late discovery of the disease In most instances the essential factor probably consists in different intensities of the pathologic process The average duration of life in chronic leukemia of all varieties is 3¼ years It is thought that about 12 per cent of cases survive more than 5 years For acute leukemia available statistics vary but in the largest series which has been studied the mean survival time from the onset of symptoms was 20 3 weeks in patients treated only with transfusions and antibiotics The longest was 58 weeks but 50 per cent of the patients were dead within 17 weeks 90 per cent within 36 weeks

In chronic leukemia treatment even though it may not increase survival time by more than 6 months or a year can for much of the time make the difference between a state of chronic invalidism and a condition of well being which may approach normality In acute leukemia the newer methods of treatment have made it possible in many instances to bring about and maintain remission in children for significant periods of time and perhaps also to prolong life In adults the results of treatment in most cases have been much less satisfactory

Prognosis in chronic leukemia can be judged more from the degree of anemia and the extent of weight loss than from the magnitude of the leukocyte count especially if these fail to respond following therapy Thrombocytopenia is also an unfavorable sign for except in occasional cases of chronic myelocytic leukemia this indicates extensive infiltration of a degree not likely to be greatly influenced by treatment

TREATMENT

Although cure of leukemia has not been achieved as yet present day methods of therapy provide considerable improvement reduce morbidity and may even prolong life as outlined above In addition to irradiation and chemotherapy which will be considered below *general measures* of management are important These include blood transfusions when necessary and antibiotics The latter are often not needed if only leukopenia is present they are better reserved for prompt use at the first sign of infection Good oral hygiene is important as well as a well balanced nourishing diet Advice concerning rest and activity should be guided by the make up of the patient In general patients with leukemia should be encouraged to maintain their normal activities in so far as possible treatment should be provided with the object of reducing morbidity and hospitalization should be reduced to a minimum

Irradiation This is of value in chronic leukemia and may be given by means of roentgen rays radioactive phosphorus (P³) *radium thorium* X or mesothorium Only the first two are now used *Increasing anemia loss of weight pressure symptoms* invasion of tissues with production of pain or disfiguring or uncomfortable glandular enlargement are indications for treatment These are of more importance than a high or rising leukocyte count While hemorrhagic manifestations and thrombocytopenia like anemia may be due to marrow infiltration by leukemic cells and thus may be alleviated by treatment more often they are part of the terminal picture of chronic leukemia and indicate that *treatment is likely to be ineffective* Acute leukemia is another contraindication to irradiation Such treatment is not only of little or no value but may be harmful

Although roentgen therapy has been the generally accepted form of *radiation therapy the choice between* this and treatment with P³ is mainly a matter of availability and convenience The details of dosage are matters for the specialist Serial daily doses of 100 to 200 r or as little as 25 to 50 r appropriately filtered and over specified areas are used by various workers Treatment is stopped when the leukocyte count has fallen to approximately 25 000 per cubic millimeter but this is not an absolute criterion since irradiation given cautiously may prove effective even in cases with leukopenia

Treatment with phosphorus made radioactive (P³) offers the advantage that the radioactive material is concentrated in the position where it is especially required—that is in those tissues which have a high phosphorus content and metabolize phosphorus rapidly the liver spleen kidneys and bone marrow The material can be given orally or intravenously and unlike roentgen irradiation it does not result in radiation sickness

There is good evidence that actual prolongation of life can be achieved with regularly spaced irradiation designed to keep the patient in a good state of health and at his normal occupation There are few now who hold to the view that irradiation *therapy or chemotherapy for that matter* should be reserved for use only in well established relapse or when symptoms are prominent

Chemotherapy Chemotherapy besides being less expensive than roentgen ray therapy as a rule makes management practical for those patients who do not reside where roentgen therapy apparatus is available Many roentgenologists employ daily treatments for 2 to 3 weeks which may be inconvenient as well as expensive in some cases A variety of chemotherapeutic agents is now available which can be taken orally Observations on *patients treated* with such agents may be spaced at intervals of one to several weeks thus permitting a return to normal activities and reducing cost In the last analysis however treatment must be designed to suit the individual needs of the patient d often both

Table 108 RELATIVE VALUE OF DIFFERENT AGENTS IN TREATMENT OF LEUKEMIAS AND LYMPHOMAS

	Chronic leukemia		Acute leukemia			Hodgkin's disease	Lymphosarcoma
	Myelocytic	Lymphocytic	Myeloblastic	Monoblastic	Lymphoblastic		
Irradiation							
Roentgen ray	++++	++++	0	0	0	++++	++++
Radioactive phosphorus	++++	+++	0	0	0	+	++
Chemotherapy							
Nitrogen mustard	+	+	0	0	0	++++	++
Triethylenemelamine	+	++	0	0	0	+++	++
Chlorambucil	+	+++	0	0	0	+	++
Urethan, demecolcin	++	0	0	0	0	0	0
Myleran	++++	0	0	0	0	0	0
Antifolic acid compounds	0	0	++	+	+++	0	0
Cortisone, prednisone	0	++	0	0	++++	+	++
6-Mercaptopurine	+	0	+++	++	+++	0	0

irradiation and chemotherapy are required at different times in the same person Thus disfiguring and uncomfortable adenopathy or great splenomegaly may call for local roentgen therapy whereas systemic manifestations are well handled by chemotherapy or radioactive phosphorus

In general the chemotherapeutic agents useful in the treatment of chronic leukemia differ from those valuable in acute leukemia (Table 108)

Chronic Leukemia Chemotherapeutic agents include Myleran (a sulfonic acid ester 1 4 dimethanesulfonyloxybutane) demecolcin (desacetyl methylcolchicine) chlorambucil [*p* (di 2 chloroethyl) aminophenylbutyric acid] and triethylene melamine

Although the nausea and vomiting associated with *nitrogen mustard* therapy (p 1226) can be allayed considerably by sedatives or an antiemetic such as chlorpromazine the discovery of other agents equally or more effective without such unpleasant action makes it unnecessary to use this drug Similar to nitrogen mustard in pharmacologic effects is *triethylenemelamine* which can be given orally and rarely causes gastrointestinal symptoms This agent is a potent hematopoietic depressant and must be used with great caution It is most useful in chronic lymphocytic leukemia For the myelocytic variety other less toxic agents are available Daily administration for a week or more seems unwise since the depressant effect is cumulative It is better to give the agent over a period of 1 to 3 days waiting then for 2 or 3 weeks before more is given so that its full effect can be determined As little as 1 or 2 mg may produce a fall in the leukocyte count and reduction in lymphadenopathy in chronic lymphocytic leukemia although 5 and rarely even 10 mg may be required The drug is usually given on awakening in the morning together with 2 Gm sodium bicarbonate Breakfast may be taken 2 hr later

Also useful in the treatment of chronic lymphocytic leukemia is *chlorambucil* an aromatic mustard 0 1 mg/kg/day by mouth This agent may be less toxic than triethylenemelamine

Myleran appears to be the most useful of the chemotherapeutic agents for chronic myelocytic leukemia In oral doses of 4 to 6 mg daily its use is associated with a reduction in the leukocyte count in the course of several weeks and a rise in hemoglobin together with corresponding clinical improvement Thrombocytopenia and purpura are the chief toxic manifestations but these are uncommon Only rarely is there any gastric discomfort When the leukocyte count has decreased to approximately 10 000 per cubic millimeter treatment is stopped Remissions measured in months have been observed Demecolcin Colcemide (an alkaloid isolated from colchicum) also is effective in chronic myelocytic leukemia The oral dose is 4 to 6 mg daily However relapse occurs promptly unless the drug is continued

Urethan 1 to 6 Gm daily by mouth has proved to be of value in many cases of chronic myelocytic leukemia but is much less useful than Myleran Nausea and anorexia may be produced by the drug The amount which is required to achieve clinical improvement may total 150 Gm However smaller amounts (0 5 to 2 Gm daily) will serve for maintenance therapy or the drug may be given intermittently

These agents as already indicated will bring symptomatic relief in many cases of chronic leukemia lymph nodes will decrease in size the spleen will become smaller anemia will decrease or dis

appear weight will be gained and a sense of well being will return to remain for variable lengths of time For the treatment of chronic lymphocytic leukemia chlorambucil is perhaps the best of the chemotherapeutic agents available at present For chronic myelocytic leukemia Myleran is the most satisfactory drug but Colcemide is sometimes effective when Myleran fails They have little value in the lymphocytic form

Splenectomy has been helpful in occasional cases of chronic lymphocytic leukemia when there was severe anemia associated with a reduced survival time of transfused red corpuscles even in the absence of frank signs of hemolytic anemia In such cases the steroid hormones cortisone and prednisone and adrenocorticotropic hormone have also been useful and they should therefore be given a trial before splenectomy is considered

Acute Leukemia In acute leukemia roentgen therapy is of no value radioactive phosphorus has limited application and the above mentioned chemotherapeutic agents are of no benefit Nitrogen mustard will reduce the leukocyte count and may relieve bone pain but offers nothing more On the other hand the steroid hormones the folic acid antagonists and other agents such as 6 mercapto purine are valuable in many cases

The steroid hormones of which *prednisone* and *cortisone* are preferable since they can be adminis tered by mouth have been found to bring about a remission in approximately two thirds of the cases of acute lymphoblastic leukemia in children and perhaps in half this proportion of adults To achieve these results usually a dose must be given which is large enough to produce signs of hyper corticism generally 100 to 200 mg cortisone or 40 to 60 mg prednisone daily Such treatment should be supplemented by potassium chloride (2 to 6 Gm daily) and the diet must be salt free A similar beneficial effect is not observed in myelo blastic or monocytic leukemia in fact these types may even be made worse Once a remission has been attained steroid therapy is stopped The re-mission may last several weeks or sometimes months One may attempt to prolong the remission by the administration of a folic acid antagonist Re treatment with steroid hormones may produce a second remission but this is usually less complete than the first

A variety of folic acid antagonists is available but *Amethopterin* (Methotrexate 4 amino N[10] methylpteroylglutamic acid) and *Aminopterin* (4 aminopteroylglutamic acid) are more generally em ployed The daily oral dose range of Amethopterin is 1 25 to 5 0 mg rarely more while that of Amino pterin is 0 5 to 2 mg The drug is given until a remission has been produced or severe toxic symp toms occur oral ulceration anorexia nausea vomiting and diarrhea leukopenia increasing thrombocytopenia and hemorrhage and increasing anemia alopecia and skin rash Sometimes it is very difficult to distinguish between toxic effects and an increase in the signs of leukemia When given in large enough doses the antagonists will lead to the appearance of megaloblasts in the bone marrow In children with Amethopterin as with cortisone remissions have been observed in approxi mately 60 per cent of those treated in adults these agents are much less successful Ultimately *resistance develops in all cases and the drugs be* come no longer effective

Of the other analogs of folic acid purines py rimidines and amino acids which have been studied with the object of discovering additional anti leukemic agents 6 *mercaptopurine* (6MP Purine thol) is the most clearly useful agent Good clin ical and hematologic remissions have been observed in somewhat less than 50 per cent of children with acute leukemia and in about 25 per cent of adults Remissions have lasted from 1 to 10 months and have been observed even in patients who had be come resistant to folic acid antagonists or to the steroids The usual therapeutic dose is 2 5 mg per kg body weight per day by mouth Sometimes twice this amount is given for a short time but in such cases the danger of producing marrow hypoplasia must be kept in mind This drug has also been found to produce improvement in early chronic myelocytic leukemia and occasional beneficial ef fects have been observed in the terminal acute stage of chronic myelocytic leukemia Such remis sions however have usually been of short duration

The most effective method for the treatment of acute leukemia is to use one agent at a time and to follow this with another one of the agents which has been shown to be effective Thus in the man agement of a case of acute lymphoblastic leukemia one might initiate treatment with steroids this be ing continued until a remission has been produced Therapy is then interrupted and the patient is observed at weekly or fortnightly intervals until the first suggestion of relapse appears Many give main tenance therapy with one of the chemotherapeutic agents but the need for this has not been proved convincingly When beginning anemia thrombo cytopenia fever sternal tenderness an occasional immature leukocyte in the blood or any other evi dence of beginning relapse appears either a folic acid antagonist or 6MP is administered until a new remission has been achieved If the remission is complete treatment may be again interrupted and is resumed when evidence of relapse once again be gins to appear this time the third agent either Amethopterin or 6 mercaptopurine being used

Later still any one of these agents may be tried again By such a plan of alternating use of drugs the development of "resistance" to one of these agents may possibly be delayed and it may be possible to prolong the life of the patient In cases of acute myeloblastic or monocytic leukemia the steroid hormones are of no value as already mentioned and treatment must depend on the antifolic acid compounds and 6-mercaptopurine The chief merit of still other agents now under study such as azaserine is that they may be employed either alone or together with the more promising drugs when the latter have spent their usefulness

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219 DISEASES OF THE SPLEEN AND RETICULOENDOTHELIAL SYSTEM

M M Wintrobe

The functions of the spleen were outlined in an earlier chapter (p 225) Disorders of the spleen most frequently produce enlargement of this organ The significance of splenic enlargement has been considered already and the differential diagnosis of splenomegaly was discussed there (p 226) Here several of the disorders which involve the spleen in particular will be described

Disorders of the spleen not hitherto considered include congenital anomalies rupture and infarction *Congenital anomalies* may take various forms Instead of being a single organ, the spleen may be subdivided into numerous small spleens or a spleen of normal size and shape may be accompanied by one or more accessory spleens Rarely the spleen assumes a retroperitoneal position and may force the left kidney downward A *movable* spleen may be found in any part of the abdomen If its pedicle becomes twisted there may be sudden pain, enlargement and signs of shock, as well as fever and vomiting if the torsion has developed acutely Less severe symptoms occur if the process is more gradual

Rupture of the spleen may occur following trauma particularly if the spleen is diseased Malaria typhoid fever and infectious mononucleosis are among the diseases in which this has been observed Agonizing abdominal pain or pain in the left scapular region, together with signs of internal hemorrhage characterize this catastrophe Anemia develops rapidly and leukocytosis occurs Prompt surgical treatment is imperative After traumatic rupture autotransplantation of splenic tissue (*splenosis*) sometimes occurs

Infarction of the spleen may be sterile in which event it is followed eventually by fibrosis and shrinkage This has been observed as a complication of leukemia A septic infarct may terminate with the formation of an abscess The most common symptom of infarction is pain Careful examination will reveal a friction rub Unless an abscess forms necessitating surgical intervention, sedation and abdominal support to impair movement of the spleen suffice

Congenital absence of the spleen may be suspected when Howell Jolly bodies occasional nucleated red cells target cells decreased osmotic fragility siderocytosis leukocytosis and a variable degree of thrombocytosis are found in the absence of a discoverable cause and particularly when there

is associated congenital heart or intestinal malformation

CHRONIC CONGESTIVE SPLENOMEGALY

Definition This syndrome also called Banti s syndrome or splenic anemia is characterized by splenic enlargement leukopenia anemia and often thrombocytopenia a tendency to gastric hemorrhage and in many cases cirrhotic changes in the liver

History The term *splenic anemia* was originally used (1866) to refer to cases of anemia with splenomegaly which were not frank leukemia Banti in 1882 and subsequently described a form of splenomegaly of unknown etiology associated in its earliest stages with leukopenia asthenia and occasional hemorrhagic episodes In the intermediary stage hepatic enlargement occurred as well as urobilinuria and a dirty brownish discoloration of the skin The final stage consisted of liver atrophy and ascites

Etiology Banti described the spleen as being characterized by conspicuous thickening of the fibrillar reticulum in the Malpighian corpuscles and red pulp (fibro adenie) These changes originated around the central artery of the follicle In his opinion the spleen was the primary seat of the disease Later work showed that these changes are not specific and can be encountered particularly when there is increased venous pressure in the portal bed Thus the designation *chronic congestive splenomegaly* has arisen Cirrhosis of the liver cavernous transformation of the portal vein portal vein and splenic vein thrombosis or variants in the anatomy of the venous pattern have been found in as many as 60 per cent of the cases Active congestion in the spleen in the absence of venous obstruction has also been proposed as a cause of this syndrome This concept depends on the hypothesis that disease of the splenic arteries is the primary fault with the result that they fail to control the amount of blood entering the spleen thus permitting congestion to develop

Pathology The spleen weighs 600 to 1 200 Gm as a rule but may weigh as much as 5 000 Gm At first one finds an increase in the reticulum cellular hyperplastic pulp degenerative changes in the follicular arterioles and congestion Later the follicles become smaller while fibrosis of the reticulum trabeculae and capsule increases Periarterial hemorrhages and siderotic nodules deposited in the fibrous tissue around the arterioles are found in many instances

Symptoms Young adults are most frequently affected but the disease may come on in childhood The onset is usually insidious The condition may ultimately attract attention in a variety of ways There may be gastrointestinal complaints of vague character probably attributable to the large mass in the left upper quadrant the mass itself may be noticed accidentally symptoms of anemia may become prominent or the disorder may be announced explosively by the occurrence of a gastric hemorrhage The spleen may extend to the pelvic brim Ultimately the symptoms and signs of cirrhosis of the liver appear Obstruction of mesenteric veins may lead to the development of hemorrhoids while occlusion of the portal vein is followed by the appearance of signs of collateral circulation

The anemia is normocytic and moderate in degree unless hemorrhage has occurred when it may be microcytic hypochromic in type In cases with long standing and severe liver disease the anemia may be macrocytic Leukopenia is found consistently and thrombocytopenia is observed frequently The bone marrow may show no abnormality or slight myeloid hyperplasia may be present

Diagnosis Other conditions leading to pancytopenia (p 1210) must be excluded Hereditary spherocytosis is not associated with leukopenia as a rule and may be distinguished also by the finding of reticulocytosis increased hypotonic saline fragility and the presence of spherocytes Hookworm infection may produce chronic hypochromic anemia with moderate splenomegaly Liver function should be studied in suspected cases and esophageal varices looked for If liver function is good and other conditions have been excluded portal or splenic vein thrombosis should be suspected Congestive splenomegaly due to extrahepatic causes is more likely to be found in patients below the age of eighteen than in older patients

Prognosis and Treatment Unless serious hemorrhage ensues the course of the disease is slow as a rule and relatively benign Patients may live for 10 years or longer The chief nonsurgical procedures are administration of a diet rich in protein and otherwise complete as well administration of iron if there has been hemorrhage and blood transfusion if bleeding has occurred recently If there is gastroesophageal bleeding abdominal exploration is advisable since some cause for congestion in the portal bed may be discovered and treated At one time splenectomy was the sole surgical measure employed However although this procedure is likely to relieve the leukopenia—and thrombocytopenia if it is present—it is of little value in relieving the portal hypertension Now therefore it is considered that a surgeon should not perform splenectomy in congestive splenomegaly unless he is prepared to form a venovenous anastomosis with the object of reducing the increased pressure in the portal bed Portacaval shunt is usually preferred because of the large size of the vessels involved If

a large-caliber splenic vein is available or when the portal vein is obliterated splenectomy and splenorenal shunts are recommended When an adequate shunt cannot be made esophagogastrectomy is employed Following removal of the spleen the leukopenia disappears the anemia is relieved in whole or in part and the platelet count is also likely to be restored to normal

GAUCHER S DISEASE

Definition This is a rare chronic familial disorder characterized by marked splenomegaly and often also by skin pigmentation pinguecular of the scleras and bone lesions

Etiology Morbid Anatomy and Pathogenesis The disorder usually is apparent early in life It has a predilection for females and the condition has been observed most often in Jewish families The characteristic finding is widespread reticulum cell hyperplasia these cells being filled with kerasin Consequently Gaucher s disease is classed as a disturbance of lipoid metabolism The cause is unknown The cells are distinctive being 20 to 80 μ in diameter round oval or spindle shaped and possessing one or more small eccentrically placed nuclei Appropriately stained the cytoplasm shows numerous wavy fibrillae These cells are found in the spleen, bone marrow lymph nodes and liver The spleen may weigh as much as several thousand grams

Symptoms The enlargement of the spleen is usually the outstanding manifestation sometimes the only one There may be a dragging sensation or pain due to infarction Pain in the limbs due to bone involvement may develop The liver may be enlarged but the lymph nodes usually are not palpable Roentgenograms may reveal osseous changes Hemorrhage from the nose or gums is relatively common Light yellowish brown discolorations on the conjunctivas on either side of the cornea and an ocher-to-brown hue of the skin, may be present.

As in other splenic disorders moderate anemia, leukopenia and thrombocytopenia are the usual blood findings

Diagnosis Diagnosis can be made by sternal or splenic puncture which will reveal the characteristic cells

Treatment and Prognosis Although the disease coincidently involves other parts of the reticuloendothelial system splenectomy is worthwhile if the spleen is very large and thereby causes discomfort or if there are serious symptoms attributable to the blood changes In infants the prognosis is not good but those who have survived to adolescence may live for many years even if splenectomy is not performed

NIEMANN PICK DISEASE

This is a lipoid disorder of the reticuloendothelial system very similar to Gaucher s disease except that the condition has been observed only in infancy and its course is much more acute death occurring within a few months after birth The characteristic cells are filled with small round hyaline droplets grouped in clusters and giving the appearance of a honeycomb The stored material is a phospholipid, perhaps sphingomyelin

HAND SCHULLER-CHRISTIAN DISEASE

Exophthalmos diabetes insipidus and defects in the membranous bones form the triad which characterizes Hand Schuller Christian disease At one time the manifestations of this disorder were considered to be produced by the growth of a characteristic type of granulation tissue with cells containing cholesterol and it esters The present tendency is to regard Schuller Christian disease as being closely related to Letterer Siwe disease and to eosinophilic granuloma *Eosinophilic granuloma* is a disorder localized to bone consisting of solitary or multiple osteolytic lesions but with no discernible visceral involvement It is found in infants children and young adults and occasionally at a later age and is treated satisfactorily by curettement or roentgen therapy *Letterer Siwe disease* has been observed exclusively in infants and young children, is variable in duration (a few weeks to several years) and has been almost uniformly fatal The three conditions possess as a common denominator a distinctive inflammatory histiocytosis Some regard Letterer Siwe disease as the acute or subacute form of a disorder of which the Schüller Christian picture is the chronic counterpart The onset of the latter is in children and in young adults The histiocytosis or granulomatosis may or may not be accompanied by intense eosinophilic reaction the characteristic lipogranuloma is now thought to be the late phase in the evolution of the histiocytic lesion Unlike Gaucher s disease and Niemann Pick disease there is no family predilection and splenomegaly and hepatomegaly do not always occur and are never conspicuous The blood may show pancytopenia Death may not ensue for many years but considerable disability may occur in the interval

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220 HODGKIN S DISEASE AND OTHER "LYMPHOMAS

M M Wintrobe

In an earlier chapter (p 223) the causes of lymph node enlargement were discussed and their differential diagnosis was considered In this section *the clinical manifestations of Hodgkin s disease and* of other conditions chiefly affecting lymph nodes such as lymphosarcoma will be described These disorders will be considered under one heading because their clinical manifestations are very similar

Definition Hodgkin s disease lymphosarcoma giant follicular lymphoblastoma (lymphoma) and reticulum cell sarcoma are included in this group They are characterized by painless progressive enlargement of lymphoid tissue Lymphadenopathy is a characteristic feature and the spleen is frequently enlarged Cachexia anemia and in many *instances fever usually are late symptoms*

History A disorder affecting the absorbent glands and spleen" was described by Hodgkin in 1832 *Lymphoblastoma malignant lymphogranuloma* and many other terms were used in referring to the disease in subsequent descriptions Jackson and Parker attempted to classify the disorder in three categories—paragranuloma granuloma and Hodgkin s sarcoma The picture of lymphosarcoma was described by Kundrat in 1893 while Brill Baehr and Rosenthal differentiated giant follicular lymphoblastoma in 1925 Roulet (1932) separated reticulum cell sarcoma from the general group of *malignant diseases of lymphoid tissue Some pa*thologists differentiate still other groups or call these by other names others seek to avoid fine separations

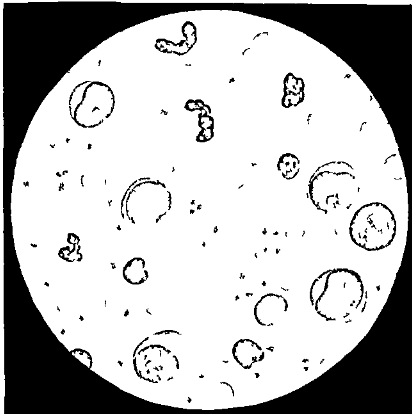
Classification Clinically these disorders vary considerably in severity Histologically they show marked differences but these are not well correlated with the clinical picture They have been classified in various ways on histologic grounds *One of the most simple is that which differentiates* those conditions with a simple histologic pattern from those with more complex patterns In the first category are reticulum cell sarcoma and lymphosarcoma The proliferating cells tend to encroach upon obscure and finally replace the architecture of the lymph node The histologic pattern of Hodgkin s disease is more complex Lymphocytes plasma cells granulocytes (eosinophilic and neutrophilic) monocytes fibroblasts and giant cells make up the picture The giant Reed Sternberg cells 10 to 40 μ in diameter are possessed of abundant cytoplasm a multilobed nucleus or multiple nuclei and prominent nucleoli A variable amount of fibrosis may be present and the lymph node architecture is often lost In giant follicular lymphoma the histologic pattern is also somewhat complex but the striking feature is the presence of multiple folliclelike nodules of various sizes Other types of lymphoma" *are observed from time to time which are difficult to classify*

Etiology Hodgkin s disease forms about one third to one half of all cases of this group It affects a younger age group than the other conditions being most common in the second and third decades However no age is immune Males are more frequently affected than females

The cause of these disorders is unknown There may not even be the common denominator of neoplastic growth to unite them for many investigators consider Hodgkin s disease to be an infectious granuloma Efforts to transmit the disease to animals have failed however and attempts to incriminate various organisms including the tubercle bacillus human and avian diphtheroid bacilli and *Brucella* organisms have not succeeded An agent *in the lymph nodes found to produce encephalitis* on inoculation into animals appears to be a nonspecific chemical substance derived most probably from eosinophilic leukocytes The other disorders in this group are assumed generally to be true neoplasms This applies even to giant follicular lymphoma which at first was considered a benign disease

Symptoms In most cases lymph node enlargement usually cervical is the first symptom to attract attention This may be bilateral but is more often unilateral at first More rarely the axillary or the inguinal nodes are the first to enlarge The *nodes are discrete and movable at first* only later do they become matted together and fixed As a rule they are painless and not tender and the overlying skin is normal However when they have developed rapidly or when nerves are infiltrated as well they may be painful This is true in Hodgkin s disease especially The size of the nodes ranges from that of a pea to that of a large orange There is a resilient firmness in most instances but the *growth of connective tissue may make the nodes of* Hodgkin s disease harder in the course of time Occasionally the nodes in the axillary or inguinal regions may become secondarily inflamed and even break down

After an interval varying from months to years evidence appears of lymph node involvement elsewhere This may affect other superficial nodes



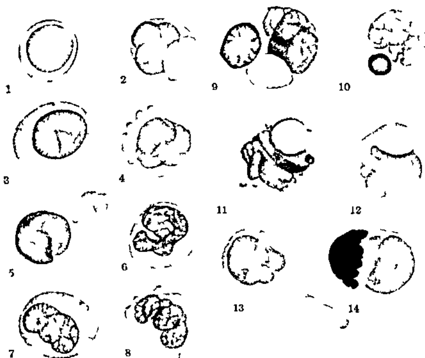


PLATE III

(*Top*) Acute leukopenic myelogenous leukemia (WBC 3 000) Film from buffy coat Actual field Five myeloblasts several showing nucleoli (*Lower left*) Promyelocyte Three nonsegmented neutrophils practically destitute of granule (toxic-degenerative changes) (*Lower right*) Two megakaryocyte nuclei with shreds of platelet material attached (*Bottom*) Cell from case of acute monocytic leukemia (1 to 14) Monocytes (1 and 3) Monoblasts (*Stitt Clough and Branham "Practical Bacteriology Hematology and Parasitology 10th ed New York The Blakiston Division McGraw Hill Book Company Inc* 1952)

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supraclavicular axillary inguinal subpectoral brachial or femoral A common site also is the mediastinum to which such symptoms as cough dyspnea stridor or dysphagia should attract attention Splenomegaly develops in more than half the cases of Hodgkin s disease and of giant follicular lymphoma less frequently in the other forms The liver is often palpable Ultimately cachexia develops and weight loss occurs

The mode of onset of these disorders may vary greatly however The manifestations may arise first in the mediastinum the lungs the digestive tract the genitourinary tract the bones and rarely the nervous system Infiltration of the lungs atelectasis or pleural effusion may occur In the gastrointestinal tract the tumor may be far advanced before it is first discovered Colicky pain loss of weight anemia a palpable tumor and obstruction are signs produced by lymphosarcoma of the small intestine When the retroperitoneal nodes are the chief ones to enlarge the diagnosis may be very difficult to make and the chief symptoms may be fever pain and loss of weight Hematuria pyuria or pain are found when the genitourinary tract is involved Localized pain and tenderness spontaneous fractures and neurologic changes due to extension into the spinal canal from vertebral lesions are the most common manifestations of bone involvement Areas of rarefaction may be demonstrable in roentgenograms although symptoms may be present long before roentgenographic signs become evident Subperiosteal infiltration may occur or the bone marrow involvement may be extensive Of cutaneous manifestations pruritus is the most frequent and this is encountered particularly in Hodgkin s disease Brownish skin pigmentation herpes zoster and nodules produced by infiltration by the specific cells are among other skin manifestations which may be encountered Symptoms and signs may also develop which are secondary to swellings producing pressure in various areas

Constitutional symptoms may appear early in Hodgkin s disease but they occur late in the other lymph node disorders Hodgkin s disease in particular may produce a great variety of manifestations so that in addition to the localized form which is much the most common a generalized type an acute type with death in a few weeks or months a "larval or abdominal form and a splenomegalic type have been described in addition to those already discussed

Fever is common in Hodgkin s disease although the well known Pel Ebstein type of fever is actually uncommon appearing no oftener than in 16 per cent of cases This form of fever consists of febrile periods of several days to several weeks duration in which the temperature remains at levels of approximately 102 to 104 F alternating with periods of weeks to even months during which there is no fever whatever

Blood Picture The greatest degree of variation is found in the blood picture associated with these disorders There may be no changes whatever On the other hand there may be profound anemia as well as striking changes in the leukocytes and platelets In Hodgkin s disease changes in the blood occur relatively early The anemia in Hodgkin s disease is usually only moderate in degree and normocytic in type very occasionally hemolytic anemia develops The total leukocyte count in Hodgkin s disease may be slightly or moderately increased it may be normal or there may be leukopenia Sometimes the leukocyte count may exceed 25 000 per cubic millimeter The differential count may show neutrophilia relative and absolute lymphocytopenia monocytosis or eosinophilia All these changes may be present at the same time or none of them Eosinophilia which is mentioned frequently as characteristic of Hodgkin s disease and which may sometimes be very pronounced is found only in about 20 per cent of cases An absolute increase in the number of lymphocytes suggests some disease other than Hodgkin s Neutropenia suggests extensive bone marrow or splenic involvement

The leukocyte picture in the other forms of disease chiefly affecting lymph nodes is more frequently normal than is the case in Hodgkin s disease Relative and even absolute lymphocytosis may be seen The lymphocytes may be of normal types but unusual forms and tumor cells" (p 1216) have been described Monocytes may be increased in number and young forms may be seen but a consistent and characteristic picture has not been described

The platelet count may be increased in Hodgkin s disease and large bizarre forms may be seen It is more common however to find the platelet count normal In some instances thrombocytopenia is present this usually occurs when leukopenia is found as well The presence of thrombocytopenia suggests extensive bone marrow or splenic involvement and is usually although not necessarily a grave sign

Bone Marrow Picture As would be expected from this description of the blood findings changes in the bone marrow are not characteristic and are seldom helpful except in rare cases of so called "bone marrow Hodgkin s in which there is extensive involvement of the bone marrow Reed Sternberg cells have been demonstrated in the bone marrow in a few cases of Hodgkin s disease Lymphocytosis may be found in the bone marrow in some cases of lymphosarcoma and of giant follicular lymphoma Such cases raise serious doubt as to whether there is any true difference between them and chronic lymphocytic leukemia

produces little or no nausea and vomiting In Hodgkin s disease 10 to 15 mg may be given in a course and maintenance doses of 5 to 10 mg per month have been employed Lymphosarcoma like chronic lymphocytic leukemia is more sensitive and 2 to 5 mg may produce an effect Other lymph node disorders may require amounts intermediate between these quantities However the potential hematopoietic depressant action limits its usefulness

Urethan Myleran and the folic acid antagonists offer little or nothing in the treatment of the lymph node disorders under discussion and the steroid hormones are only occasionally and transiently useful The effects of irradiation and various chemotherapeutic agents are compared in Table 108 (p 1219)

In addition to these measures general supportive and symptomatic therapy will be required in individual cases

Prognosis The most important factor which seems to determine the course of these disorders is their inherent character Cases of Hodgkin s disease and of lymphosarcoma are known to have run a chronic course for many years In other instances the course is rapid and progression occurs in spite of therapy In general cases with the most favorable outlook are those in which only one accessible lymph node group is affected and where evidences of systemic involvement such as fever loss of weight increased sedimentation rate and changes in the blood are lacking In the last analysis a therapeutic trial should be attempted for a prolonged remission mav sometimes be encountered even in cases in which the general examination suggests a hopeless prognosis

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221 MULTIPLE MYELOMA

M M Wintrobe

Definition Multiple myeloma is characterized by the development of multiple tumors of bone which produce pain pathologic fractures and anemia There may be diffuse involvement of the bone marrow and in the urine or blood a peculiar protein is usually found Rarely a localized tumor is the only manifestation Tumors composed of other types of cells have been described but the evidence is all in favor of a single type ("myeloma" or plasma cell)

Etiology The disease appears most commonly after the age of forty and is twice as frequent in males as in females The cause is unknown The true nature of the peculiar protein is not clear It is presumed that the myeloma cell is responsible for the protein anomalies of multiple myeloma This cell has the cytochemical characteristics of an intensely protein producing cell as judged by ultraviolet microscopy Protein with ultracentrifugal and electrophoretic properties similar to those of the abnormal components present in the plasma in this disease has been extracted from myeloma tumor tissue Some investigators hold however that rather than being a neoplastic growth multiple myeloma is due to a derangement in protein metabolism

Symptoms Pain is the most frequent complaint and is produced by the tumors which according to their location may or may not be discoverable on physical examination The tumors range from the size of a pea to that of a hazelnut They are confined for the most part to the sites of the red marrow the ribs sternum spine clavicles skull or the extremities about the shoulder or pelvic girdle Roentgenograms reveal discrete punched out lesions osteoporosis and pathologic fractures Deformity and neuralgic or neurologic symptoms may develop Less frequently anemia abnormal bleeding or symptoms suggesting nephritis are the chief manifestations

Laboratory Findings Anemia is moderate in degree as a rule and normocytic but sometimes it is severe and macrocytic Enumeration of the cells may be difficult because of clumping a peculiarity often related to the great quantity of globulin in the plasma In blood smears there may be a marked tendency to rouleaux formation Polychromatophilia stippling and even normoblasts may be found in the blood smear The leukocyte count may be normal slightly increased or low Myeloma cells like those seen in the bone marrow may be found The platelet count is usually normal

Hyperproteinemia may be present (50 to 65 per cent of cases) and sometimes extremely high values are found The increase is due to the globulin fraction Sometimes the protein precipitates or coagulates spontaneously when the plasma is exposed to low temperatures (cryoglobulin) Its presence may be associated with a variety of symptoms especially those suggesting the Raynaud syndrome Detailed studies have revealed that the type of

Diagnosis The differential diagnosis of lymph node enlargement was discussed in an earlier chapter (p 224) Cases in which there is little or no enlargement of the superficial lymph nodes present the most difficult problem in diagnosis for then a variety of inflammatory and neoplastic disorders of the mediastinum lungs gastrointestinal tract or liver must be considered and the possible presence of chronic infections such as brucellosis must be ruled out Hodgkin s disease in particular may produce such varied manifestations that this disorder must be kept in mind almost whenever diagnosis is obscure This disease is particularly suggested by such symptoms as relapsing fever loss of weight and splenic or hepatic enlargement together with anemia and leukocytosis or leukopenia

Treatment Surgical excision irradiation and chemotherapy all have their place in the treatment of these disorders Surgery is useful when the condition is definitely localized irradiation is effective in the treatment of local manifestations and when the disease is generalized and chemotherapy is particularly indicated when the disorder is widespread Sometimes all three forms of therapy can be employed and frequently there are advantages in using both irradiation and chemotherapy

Since these conditions in many instances appear to arise locally and only disseminate later *surgical excision* should be an excellent form of therapy Unfortunately correct diagnosis is not often made early Furthermore in many instances in which the disease seems to be local dissemination has already occurred or has been present from the beginning Nevertheless this form of therapy when appropriately applied offers the only chance of cure Surgical excision if undertaken must be radical and should be followed by irradiation or chemotherapy or both Surgery should also be considered in the form of splenectomy when signs of hypersplenism are present severe anemia with shortened life span of transfused red corpuscles leukopenia and thrombocytopenia

Roentgen rays represent the preferred method of *irradiation* this apparently being somewhat superior to the use of radioactive phosphorus and more effective than radium Generally speaking segmental or localized irradiation is used rather than total irradiation except in cases in which generalization has taken place Various areas are treated in succession The decision as to dosage is the problem of the radiotherapist The total amount depends on the response of the lesions to therapy the general effects on the patient and the effect on the blood The effect of irradiation may be dramatic large masses melting away in the course of a week Pressure symptoms may disappear fever and pruritus if present may be relieved and pain caused by bone involvement may be alleviated Pulmonary lesions may decrease in size and pleural effusions may clear Anemia may disappear and the leukocyte count if elevated may drop to normal In other cases irradiation is less effective in some instances being of scarcely any benefit Prediction in advance as to the likelihood of benefit from therapy is often difficult In general the more chronic and slowly growing forms respond best to therapy Remission following treatment may last but a few weeks or may persist a year or longer In some cases such improvement can be reproduced many times by additional therapy

The action of *nitrogen mustard* in these disorders is similar to that of irradiation but in certain cases of Hodgkin s disease this drug seems to be more effective than irradiation It has been found that in some cases previously given roentgen therapy and no longer responding to such treatment nitrogen mustard therapy has been distinctly beneficial Other cases treated with nitrogen mustard from the beginning have responded well and in general in a manner similar to that already described under roentgen therapy Fever often disappears promptly and anemia if present also is alleviated Abnormalities in the leukocytes may revert toward normal although the immediate effect noticeable within 5 to 14 days following the first dose of nitrogen mustard may be leukopenia and an increase of anemia Thrombocytopenia if present at the initiation of therapy is less likely to be relieved by treatment

Nitrogen mustard [methyl bis(β chloroethyl) amine hydrochloride HN2] is given intravenously in doses ranging from 0 1 to 0 3 mg per kg body weight per injection each day As much as 0 8 mg per kg constitutes a course of therapy although the usual amount is 0 4 to 0 6 mg The drug is available in vials containing 10 mg In order to prevent thrombosis a solution of normal saline is first introduced intravenously and when this is flowing freely 10 ml saline solution is added to the vial where the drug dissolves readily The appropriate dose is withdrawn and injected through the rubber tubing of the saline infusion Nausea and even vomiting may follow several hours after injection of the drug but this is usually of shorter duration even though sometimes more intense than that seen in irradiation sickness The nausea and vomiting can be allayed or prevented by giving chlorpromazine in three 20 to 30 mg doses 6 and 4 hr before and at the time of the injection

The discovery of other chemotherapeutic agents has reduced the comparative importance of nitrogen mustard in the treatment of the various forms of leukemia and the lymphomas with the exception of Hodgkin s disease *Triethylenemelamine* (p 1219) appeared at first to be very promising because it has the advantage as compared with nitrogen mustard that it can be given by mouth and

cases Both these changes can be ascribed to the renal damage associated with the deposits of Bence Jones protein which are found not only in the distal tubules but in the entire nephron up to the proximal convoluted tubules The resulting distention and obstruction to renal flow lead to glomerular atrophy and ultimate renal failure (myeloma kidney") It is thus not unusual in multiple myeloma to find albumin casts and renal epithelial cells in the urine and evidence of renal functional impairment as well as nitrogen retention often develop

The *bone marrow* frequently contains the tumor cells although their number may range from 3 to 96 per cent The myeloma cell is moderately large (15 to 30 μ), and round or ovoid and contains a round eccentrically placed nucleus which may contain one or two nucleoli The chromatin is moderately coarse The cytoplasm is bright blue Attempts have been made to classify myeloma cells according to their maturity and to establish some correlation to the clinical manifestations of the disease Some tendency for patients with the more mature cell types to live longer and for those with greater percentages of immature cells to manifest renal involvement has been observed but extreme variations have been encountered in individual cases and no consistent correlation between cell type and extent of bone involvement hyperglobulinemia Bence Jones proteinuria or the electrophoretic distribution of the various globulin fractions has been established

Diagnosis The multiple bone lesions the excretion of Bence Jones protein the hyperproteinemia and the characteristic cells in the bone marrow form a combination of findings which makes the diagnosis evident Difficulty arises when back pain obscure anemia or some complaint of nonspecific character has failed to suggest this disease and the appropriate examinations have not been made Sometimes the picture may closely simulate hyperparathyroidism (see p 577)

Prognosis and Treatment The prognosis is unfavorable The average duration is 2 to 3 years Great variations occur however and some patients live for many years Local irradiation is often helpful and may be strikingly so if there is a single bone lesion The effects of irradiation on myeloma are rather unpredictable however Urethan is perhaps the best therapeutic agent currently available but even its value is limited Although subjective improvement is associated with its administration in about half the cases objective improvement has been observed in only about 20 per cent To achieve any benefit doses of 2 to 5 Gm daily have to be given for periods of 6 to 10 weeks With these doses nausea and vomiting may develop and may necessitate withholding the drug Other chemotherapeutic agent including stilbamidine nitrogen mustard and triethylene melamine are of even less value The effects of the steroid hormones have been disappointing

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222 OTHER DYSPROTEINEMIAS AND PARAPROTEINEMIAS

M M Wintrobe

History Definitions and Clinical Syndromes Although multiple myeloma and Bence Jones proteinuria were recognized in 1845 the presence of a cold precipitable protein in the serum of a patient with this disease (*cryoglobulin*) was not described until almost a century later (Wintrobe and Buell 1933) *Macroglobulins* high molecular weight proteins demonstrable only by ultracentrifugation and a syndrome associated with *macroglobulinemia* were described in 1944 (Waldenstrom) Since that time with the exploitation of electrophoretic ultracentrifuge and serologic techniques considerable attention has been attracted to the occurrence of aberrations in protein metabolism in association with various diseases and sometimes in the absence of any associated disorder In some instances it appears that the unusual findings represent only increases of normally occurring protein molecules (*dysprote*

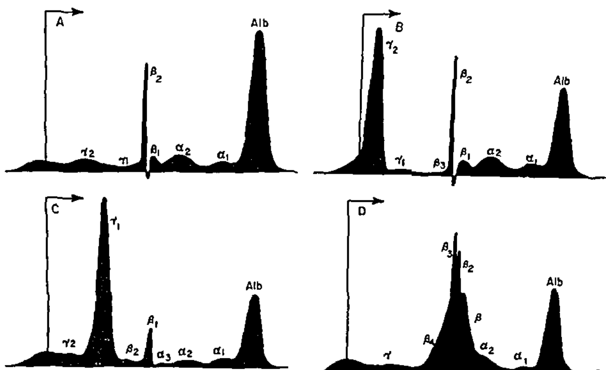


FIG 158 Descending patterns after 250 min of pooled normal serum (A) and serum from two patients with multiple myeloma (B and D) and one patient with macroglobulinemia (C) determined by electrophoretic analysis at 1 C in 0 1 ionic strength Veronal buffer at pH 8 4 to 8 5 Note the large gamma globulin component (γ) in (B) and the beta globulins in (D) as well as the gamma globulin (γ_1) in the case of macroglobulinemia (C) The very narrow β peaks in (A) and (B) are anomalies probably due to lipoproteins and are not unusual in serums from nonfasting subjects (*Courtesy Drs Emil L Smith and B V Jager and Mr Douglas M Brown*)

protein which is predominant differs from one case to another In the majority of cases gamma globulin is increased in others it is beta globulin and in the minority the substance is an alpha globulin The diagnostic patterns in multiple myeloma as measured by the Tiselius electrophoretic technique are characterized by tall narrow sharply defined peaks owing to the presence of large amounts of a relatively homogenous abnormal protein (Fig 158 *B* and *D*)

When the *urine* is heated a white cloudy precipitate appears at temperatures of 50 to 60 C but when the temperature is raised to near the boiling point the precipitate redissolves Such Bence Jones protein has been observed in 40 to 50 per cent of cases As judged by various physicochemical determinations Bence Jones proteins are related neither to normal serum proteins nor to the abnormal serum proteins As judged by serologic reactions however they appear to be related to normal serum proteins Bence Jones protein can be synthesized readily from free amino acids rather than from tissue protein precursors There is evidence that myeloma serum globulins may be conjugated glycoproteins containing a significant quantity of carbohydrate bound to the protein component In contrast the urine myeloma proteins seem to be devoid of any significant carbohydrate component

In addition to the hyperproteinemia and the Bence Jones proteinuria a third form of protein abnormality may be observed in multiple myeloma This is the deposition of a peculiar protein in the tissues producing atypical amyloidosis or *paramyeloidosis* This has been observed upon histologic examination in 6 to 10 per cent of cases of multiple myeloma

Not infrequently certain chemical changes are found in the blood *Hypercalcemia* has been observed in 20 to 53 per cent of cases values of 12 to 16 mg per 100 ml being not unusual With progression of the disease the hypercalcemia may increase The high serum calcium levels have been attributed to the resorption of bone which takes place but they are further increased by secondary hyperplasia of the parathyroids caused by renal impairment As a rule the hypercalcemia is not accompanied by a decrease in the inorganic serum phosphorus or by much increase in alkaline phosphatase thus differing from the changes found in primary hyperparathyroidism

The serum uric acid is not infrequently increased and nitrogen retention has been noted in many

Plasma cells are thought to be the source of cryoglobulins and atypical lymphocytic cells the source of macroglobulins but more primitive or more malignant precursors of these cell types are also thought to produce these unusual plasma proteins

Diagnosis Hyperproteinemia is found in most cases and is generally attributable to a great increase of globulin usually gamma globulin In most instances the globulin fraction amounts to 4 to 8 Gm per cent The Sia test which involves mixture of the patient s blood with distilled water and observation of the formation of a precipitate when positive has not been found to be a reliable screening test for macroglobulinemia The electrophoretic pattern of severe macroglobulinemia is indistinguishable from that of multiple myeloma Immunologic diagnosis with antimacroglobulin serum has been successful in most cases studied but ultracentrifugation should be carried out in suspected cases since it yields the critical evidence

The diagnosis of cryoglobulinemia offers no particular difficulty but since cryoglobulins have a wide thermal amplitude blood for these studies should be drawn into warm syringes and separation of serum or plasma carried out at 37 C Cold precipitation reversible on warming is characteristic The differential diagnosis of cryoglobulinemia should include consideration of cryofibrinogens and cold agglutinins

Macroglobulinemia should be distinguished from *purpura hyperglobulinemica* characterized by dependent purpura and hypergammaglobulinemia The characteristic electrophoretic gamma globulin peak in this syndrome is a broad hump in contrast to the sharp peak of macroglobulinemia

Prognosis and Treatment The prognosis in the secondary forms depends upon the nature of the underlying disease process The primary disorders are compatible with survival for several years If death occurs it is usually due to severe anemia complicating infections or the hemorrhagic diathesis ACTH or adrenocorticosteroid therapy has sometimes seemed to be helpful

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Section 2 The Cardiovascular System

A DISEASES OF THE HEART

T R Harrison and
William H Resnik

Of the various disorders which afflict mankind those of the heart and blood vessels assume first rank In the United States these disorders represent the single greatest cause of chronic disability and are responsible for more deaths than the next five most common causes combined As other diseases are conquered by the progress of medical science the proportion of persons living to the advanced ages at which cardiovascular diseases are most common continually increases Barring the possibility of as yet unforeseen discoveries leading to more effective prevention and treatment of these disorders it can be estimated that one third or more of the present population of the United States will die of cardiovascular disease Among males engaged in business and professions the proportion will perhaps be nearer one half

Present knowledge of cardiovascular disease rests upon the solid foundation of clinical physiology Among those who have contributed most to understanding of these disorders are William Harvey who first demonstrated clearly the circulation of the blood after this concept had been suggested by Cesalpino William Withering who introduced the

inemias) whereas other studies suggest that they denote aberrant protein synthesis (*paraproteinemia*)

Cryoglobulinemia of minor degree (less than 25 mg per cent) may be encountered in a large variety of disorders including systemic lupus erythematosus rheumatoid arthritis periarteritis nodosa chronic lymphocytic leukemia lymphosarcoma polycythemia rubra vera kala azar subacute bacterial endocarditis coronary artery disease hepatic cirrhosis and numerous other diseases Rarely the cold precipitable protein is present in large amounts and is associated with atypical Raynaud phenomena purpura bleeding from nose and mouth retinal hemorrhages cold sensitivity cyanosis mottling and even gangrene of the lower extremities Multiple arterial and venous occlusions may occur Rouleaux formation pseudoagglutination of the red cells and an elevated erythrocyte sedimentation rate are likely to be found as well In most instances of this sort multiple myeloma has been demonstrated and rarely other disorders such as chronic lymphocytic leukemia In a few instances no underlying disease entity could be demonstrated (*essential cryoglobulinemia*)

The concentration of cryoglobulin in plasma or serum has ranged from trace amounts to 10 Gm per cent The amount may vary over the course of the illness in the same patient The minimum concentration of cryoproteins required for massive reversible precipitation is about 1 Gm per cent The precipitation of the plasma protein is due to its decreased solubility in the blood and can be demonstrated in vitro The most commonly occurring cryoglobulins have been found in the gamma fraction but globulins in the alpha fraction in the beta fraction and between the beta and gamma peaks have also shown this property Molecular weights have ranged from 165 000 to 600 000

Macroglobulinemia is detectable with certainty only by ultracentrifugal analysis The molecular weight of the macroglobulins is greater than 1 million Trace amounts of macroglobulins are present in normal serums The term *macroglobulinemia* is applied to serums containing more than 5 to 10 per cent of components sedimenting with a Svedberg constant greater than 15 Pathologic macroglobulin molecules have the electrophoretic mobility of beta or gamma globulins or are intermediate between these two Occasionally an abnormal plasma protein may be both a cryoglobulin and a macroglobulin

Macroglobulinemia has been observed in the nephrotic syndrome in cirrhosis in association with malignant tumors and in congenital syphilis Serums of multiple myeloma have seldom been reported to show abnormal high molecular weight components In the syndrome described by Waldenstrom *primary macroglobulinemia* in contrast to multiple myeloma focal bone lesions are not found there being at most a diffuse osteoporosis but slight to moderate lymphadenopathy and hepatosplenomegaly are characteristically encountered Bone pain is conspicuously absent In clinical features primary macroglobulinemia thus resembles lymphosarcoma rather than multiple myeloma Symptoms and signs of vague ill health some weight loss lassitude dyspnea and recurrent infections are common as well as pallor and edema Sjogren s syndrome (dryness of mucous membranes in eye nose mouth and vagina) has been described in association with macroglobulinemia Epistaxis and mucosal bleeding are frequent Anemia usually normocytic is present leukopenia relative lymphocytosis sometimes eosinophilia or monocytosis as well as thrombocytopenia hemolytic anemia and *pancytopenia have been observed Bence Jones* proteinuria and paramyloidosis such as are seen in multiple myeloma have been reported The bone marrow characteristically shows large numbers (40 to 80 per cent) of small atypical "lymphocytic" cells with protoplasmic shedding and "naked nuclei" The erythrocyte sedimentation rate is markedly elevated Bleeding time coagulation time and prothrombin time may be prolonged and prothrombin consumption may be impaired

Pathology and Pathogenesis In the secondary forms of dysproteinemia and paraproteinemia the pathologic findings are those of the underlying disorder In the primary disorders no specific changes have been noted except for the signs of *reticuloendothelial hyperplasia and the bone marrow* and lymph node infiltration with small atypical lymphocytes which have been observed in primary macroglobulinemia When cryoglobulinemia has been present pulmonary arteriolar obstruction has been described as well as vascular occlusion elsewhere (kidneys etc) Symptoms associated with cryoglobulinemia have been attributed to precipitation of cryoprotein in peripheral blood vessels as well as to cold agglutination of red cells by this protein in vivo The bleeding tendency has been attributed to intravascular precipitations with secondary capillary damage and in some cases to defects in platelet function

No uniformity in the physicochemical characteristics of macroglobulins has been demonstrated Macroglobulin peaks in the electrophoretic diagram are sharp and cannot be differentiated from myeloma proteins (Fig 158C) Macroglobulins frequently sediment in the ultracentrifuge as multiple components Studies of their amino acid composition have *shown variations from patient to patient It* is uncertain from immunologic studies whether the macroglobulins and cryoglobulins represent increases of normally occurring protein molecules or denote aberrant protein synthesis

there is strong evidence that anxiety worry and emotional stress not only make the patient unhappy but may actually tend to aggravate the structural disorder and hence one of the prime principles in management is to attempt to remove all sources of psychic stress whether they be related to anxiety about the heart or to environmental factors concerning family business etc In the patient with cardiac as with most other chronic diseases there are many situations in which the physician himself becomes the treatment and in which happiness depends mainly and health partly on the physician s wisdom optimism tact and perhaps above all else on his willingness to devote as much time as may be required to listening to the patient s troubles and to alleviating his anxiety

Treatment of Underlying Disease Process Certain causes of cardiac disease unfortunately not the most common ones are amenable to cure Hence one of the primary therapeutic principles is to search constantly for such cases In the majority of instances these curable conditions are those associated with the clinical manifestations of high output failure (p 101) i e the signs of congestive failure occurring in association with the signs of the overactive heart When as in the great majority of patients with congestive failure such manifestations are absent one should think first of all of mitral stenosis or aortic stenosis then of constrictive pericarditis and of myxedema as possible causes In an individual with congenital heart disease the first thoughts should concern patent ductus arteriosus coarctation of the aorta pulmonic stenosis interauricular septal defect and the tetralogy of Fallot because these conditions likewise are completely or partially curable

Physical Activity A sharp distinction must be made between those patients presenting evidence of recent myocardial injury and those in whom no such evidence exists Patients with acute rheumatic carditis should be kept at complete rest and allowed out of bed only for purposes of bowel movement Patients with subacute rheumatic carditis represent a special problem After myocardiac infarction rest is indicated with the realization that prolonged bed rest carries serious hazards (p 1267)

In the absence of evidence of recent or progressive myocardial injury the problem of physical activity is different It is here that overzealous insistence by the physician on unnecessary restrictions so often creates a state of anxiety and psychic invalidism which is more disabling to the patient than the underlying structural disease In the absence of acute or recent myocardial injury there is no evidence that physical activity which can be tolerated by the patient without symptoms is harmful Hence the rule of living for such patients is a simple one and consists of living below the symptom threshold In other words *the patient should not do anything which induces pain of the anginal type or dyspnea but may carry on physical exertion which does not cause these symptoms This principle of management is probably the single most important feature of the treatment of chronic cardiac disease* for adherence to it will automatically adjust the patient s activities to things which can be done without overburdening the heart and at the same time allow all the leeway which the cardiac condition permits Moreover it will tend to prevent the development of that anxiety state which is so commonly the most important feature of the disease as far as the happiness of the patient and of his family is concerned For the appropriate patient the knowledge that he is permitted to participate in a game of golf or some other moderate form of physical exertion has a greater psychotherapeutic value than verbal assurances that have no concrete meaning to him

223 DIAGNOSTIC ASPECTS OF HEART DISEASE (Including Treatment of the Arrhythmias)

T R Harrison and William H Resnik

It should be emphasized at the outset that persons either do or do not have heart disease and that while the decision is at times difficult and rarely may be impossible there is no intermediate state Hence such terms as a heart condition a tired heart and myocardial damage which are ordinarily used to conceal the physician s uncertainty have no place in modern medicine They should be relegated to limbo along with anginoid "pseudo angina etc

Chronic cardiac disease is of two general types one characterized by pain and the tendency toward sudden death the other by dyspnea and the tendency toward congestive failure In the diagnosis of angina pectoris the commonest variety of the first type the information obtained from the history is all important as has been stressed in Chap 4

If one omits from consideration those types of cardiac disease related to disturbance of the coronary circulation and characterized by pain as the outstanding manifestation it may be stated as a general rule that the recognition of *heart disease* depends on the objective information obtained by examining the heart while the recognition of *heart failure* depends either on subjective information

use of digitalis into medical practice René Theophile Hyacinth Laennec who introduced auscultation a method so beautifully expounded in heart disease by Pierre Carl E Potain William Heberden who described angina pectoris James Hope who described the mechanism of congestive heart failure Richard Bright who first clarified the hypertensive and renal disorders Sir James Mackenzie who was the first to emphasize that the test of a heart is its response to effort Ernest Starling who established the physiologic basis of heart failure Willem Einthoven who devised the electrocardiograph James Herrick who developed the modern clinical concept of myocardial infarction Sir Thomas Lewis who exemplified the importance of critical investigation in the study of patients with cardiovascular disorders Frank N Wilson who began the clarification of the basic principles of the electrocardiogram and Myron Prinzmetal who has resolved the previous conflicts between clinical judgment and electrocardiographic interpretation These men and many who cannot be cited here were the trail blazers while the roads have been built by the innumerable contributions of others

The physician who is confronted with a patient presenting evidence of the possible presence of disease of the heart necessarily asks himself certain questions of which the most important are

1 Is heart disease present?
2 If so what type of heart disease is it?
3 How serious is it?
4 What should be done about it?

In the sections to follow an attempt will be made to consider these questions and accordingly the diagnostic etiologic prognostic and therapeutic aspects of cardiac disease will be discussed in respective sequence Since the subjects of arteriosclerosis hypertension and rheumatic fever the most common and important causes of cardiovascular disease have been considered in other chapters the discussion to follow will deal only with such aspects of these topics as are especially pertinent No attempt will be made to consider all the less common causes of cardiovascular disease and the discussion of etiology will be centered on those factors which are especially important either because of frequency or because of susceptibility to cure

The arrangement of this section on Diseases of the Heart departs from that traditionally given in discussions of the various types of cardiac disorder To avoid needless repetition of symptoms signs criteria of prognosis and methods of treatment that are common to *many forms of heart disease regard*less of etiology discussion has been arranged primarily according to the general topics of diagnosis etiology etc The fundamental principles of diagnosis prognosis and treatment are in the main similar irrespective of the basic causes of heart disease To achieve this simplicity of arrangement and avoidance of unnecessary reiteration by rigid adherence to such a program is to introduce certain disadvantages Thus angina pectoris would require separate discussions under Pain in the Chest Etiology and Treatment the arrhythmias would need consideration under Diagnosis and Treatment etc The authors believe that a strict pursuit of this plan contains inherent disadvantages that tend to nullify whatever logic resides in such an approach to heart disease Hence an attempt has been made to resolve this dilemma of presentation by combining the various aspects of congestive heart failure into a single chapter The treatment of the manifestations of heart disease other than congestive failure are taken up in those chapters where they seem naturally to fall Thus the symptoms diagnosis and treatment of the arrythmias are considered together under Diagnostic Aspects of Heart Disease (Chap 223) the special problems of symptomatology and treatment of other conditions in the respective discussions under Etiologic Aspects of Heart Disease (Chap 224) Because of the unique problems presented by congenital heart disease a special chapter is devoted to this subject

The reader may find it useful when the commoner symptoms of heart disease are mentioned to refer to previous chapters on Pain in the Chest (Chap 4) Dyspnea (Chap 10) Palpitation (Chap 13) Edema (Chap 20) Cyanosis (Chap 12) Circulatory Failure (Chap 14) etc

PRINCIPLES OF THERAPY IN PATIENTS WITH CHRONIC CARDIAC DISEASE

Psychologic Management This is of the utmost importance When grave anxiety concerning the heart exists in the absence of structural disease thorough examination coupled with tactful and time consuming reassurance plus the use of specialized psychiatric therapy when needed will usually yield strikingly gratifying results The problem becomes more difficult when as is so often the case the anxiety state occurs in a patient presenting clear evidence of a structural cardiac disorder Here again psychic invalidism can usually be avoided if the physician will refrain from frightening the patient and will take sufficient time to discuss the problem and to explain the significance of various findings Further discussion of psychologic management will be found in Chaps 13 and 41 which deal with palpitation and anxiety respectively

It is especially important that unnecessary restrictions not be imposed on patients for there is no *evidence that physical activity which does not* induce pain or dyspnea is harmful to the person with chronic cardiac disease On the other hand

Dilatation The mechanisms of cardiac dilatation have already been discussed (Chap 14) and here it need only be repeated that dilatation results from defective systolic emptying

The x ray is of the greatest value in the decision as to the presence or absence of dilatation of the several cardiac chambers Space does not permit a detailed discussion of this important subject and the reader is referred to books on radiology Briefly it may be said that dilatation of the left ventricle tends to produce some rounding of the apex as seen in the frontal projection and backward enlargement of the cardiac shadow as observed in the left anterior oblique position Dilatation of the left auricle produces a convexity of the left portion of the cardiovascular shadow in the region between the pulmonary artery shadow and the ventricular shadow but a more characteristic sign is the bulging backward of the lower posterior cardiac shadow into the retrocardiac space with displacement or compression of the barium filled esophagus when the patient is viewed in the right anterior oblique or in the left lateral position This phenomenon is characteristically seen in some patients with mitral stenosis and/or insufficiency Right ventricular enlargement tends to cause the heart to assume a more anterior position but it is often not detected by the x ray Right auricular enlargement is usually characterized by increased size to the right

The electrocardiogram is usually of little help in the diagnosis of cardiac dilatation However the occurrence of intraventricular conduction defects with widening, slurring and notching of the QRS complexes often superimposed on the signs of ventricular hypertrophy may occur This is often striking if acute dilatation occurs suddenly with overstretching of the conduction system and of the myocardial fibers The sudden appearance of records resembling right bundle branch block often lasting for a few hours only in patients with chest pain may signal the presence of a large pulmonary embolus with transient right ventricular dilatation (acute cor pulmonale) The tall spiked P waves in leads II and III in patients with chronic lung disease (pulmonary P waves) are apparently associated with auricular dilatation and displacement since they often regress with treatment of the congestive failure

Physical examination usually yields significant and often decisive information on the important question as to whether the heart—regarded as a whole—is enlarged or not Here palpation assumes the position of first importance Whether the heart is enlarged to the left can usually be determined by palpation of the point of maximal impulse Unfortunately the position of the right border cannot be determined with corresponding accuracy by clinical method for percussion possesses limited value in the examination of the heart and does not afford an accurate guide as to the position of the right border in the majority of patients However if the point of maximal impulse is outside the mid clavicular line one can be reasonably certain that the heart is either enlarged or displaced Displacement usually to the left may result from lateral curvature of the spine More commonly it is due to disorders of the pleural cavity such as hydrothorax pleural effusion or pneumothorax all of which tend to displace the heart toward the opposite side or to atelectasis and pleural thickening which tend to displace the heart toward the affected side Hence in the absence of lateral curvature of the thoracic spine cardiac displacement can usually be recognized by examining the lungs By combining careful physical examination of the lungs with accurate palpation of the heart cardiac enlargement can be established by clinical methods alone However this decision is accurate only when the apical impulse can be felt When because of age obesity or emphysema palpation of the apical impulse is impossible the x ray must be used to determine cardiac size It is a relatively inaccurate method for this purpose The most commonly used roentgenographic index of cardiac size is the transverse diameter in relation to the total diameter of the chest This method while valuable when marked alterations in cardiac size exist is of limited value in the detection of the earlier stages of enlargement and for this purpose other more complicated methods of measurement are considered to be more accurate These too have their limitations A large apical fat pad may lead to a false x ray diagnosis of cardiac enlargement

Aside from its value in affording information concerning the size of the heart the x ray is even more useful in revealing alterations in cardiac shape which by offering an indication as to the chambers and vessels particularly affected often furnish diagnostic clues which cannot be obtained by any other means

ALTERATIONS IN HEART SOUNDS

Ventricular Volume Curve in Relation to Heart Sounds In interpreting the sounds arrhythmias and murmurs observed on auscultating the heart it is helpful to relate these phenomena to the ventricular volume curve This curve is illustrated in Fig 159 and a few of the aspects in which it may be useful are indicated in the accompanying legend

The chief factors which influence the intensity of the first sound are (1) the position of the valves at the onset of ventricular systole which is usually determined by the length of time elapsing between atrial and ventricular contraction (2) the rate of

obtained from the story or objective phenomena to be found by examining the body as a whole rather than the heart Since the present chapter is concerned with the diagnosis of heart disease rather than that of heart failure (which will be considered in a succeeding chapter) the discussion to follow will center around the recognition of those objective findings which afford either suggestive or unequivocal evidence of the presence of structural cardiac change

ENLARGEMENT OF THE HEART

This is the most common objective manifestation of cardiac disease Enlargement is of two types—hypertrophy and dilatation These commonly occur together and are related intimately to each other However since they produce *somewhat different* physical signs and have somewhat different significance they will be considered separately

Hypertrophy Much has yet to be learned about the exact mechanism responsible for an increase in the cardiac muscle mass In most cases there is clear evidence that hypertrophy of the individual muscle fiber is related to increase in work brought about either as the result of an increased load on the particular chamber concerned or as the result of disease of some fibers which become less able to carry their portion of the load and hence cause the remaining fibers to have an additional burden

The bedside recognition of cardiac hypertrophy is not difficult in young slender individuals but may be impossible in older patients with emphysema or obesity In many instances simple palpation is a more delicate guide to hypertrophy than is the electrocardiogram or the x ray Since the left ventricle makes up only a slight portion (in the region of the apex) of the projection of the heart onto the anterior chest wall hypertrophy of this chamber does not give rise to a diffuse impulse *In patients with left ventricular hypertrophy the impulse is therefore sharply localized powerful thrusting and heaving* In some patients this impulse can be recognized only when the subject is lying on his left side

Other causes of an unusually powerful apical impulse are extreme right ventricular hypertrophy and an apical aneurysm due to myocardial infarction Some patients display a bulge of the apex during anginal attacks with disappearance of the bulge as the pain and presumably the apical ischemia disappear

On the other hand when the right ventricle is hypertrophied the impulse is diffuse pulsations are observed over the entire precordial area and on palpation the beat is found to be well sustained This greater duration and heaving quality of the precordial pulsations serves to differentiate right ventricular hypertrophy from the overactive heart This condition also produces increased precordial pulsations which however are poorly sustained and of tapping quality In many instances of right ventricular hypertrophy the most striking pulsation is an oblique forward and footward thrust in the left xiphochondral notch This is particularly true when as in patients with emphysema the precordial movements are dampened by the lungs

Aside from right ventricular hypertrophy and the conditions which increase cardiac output there are other states which may cause an increase in pulsations in the left parasternal region A pronounced systolic lift is sometimes observed in patients with infarction of the interventricular septum Rarely a patient with left ventricular hypertrophy only may display such an impulse which is possibly *due to forward displacement of the septum during* systole The forceful onset and abrupt cessation of filling in patients with constrictive pericarditis may produce a *diastolic* lift of the precordium which must be distinguished from the systolic heave caused by hypertrophy of the right ventricle

Since ventricular hypertrophy frequently occurs in response to an increase in peripheral resistance the closing sounds over the semilunar valves heard over the base of the heart are increased in intensity A loud second pulmonic sound may indicate pulmonary hypertension and therefore usually right ventricular hypertrophy a loud second aortic sound suggests systemic arterial hypertension and left ventricular hypertrophy This rule does not apply of course if valvular stenosis (aortic or pulmonary) is present

When the cardiac impulse is not readily visible or palpable because of obesity or emphysema the less reliable methods must be employed The electrocardiogram may give useful information as to which ventricle is hypertrophied provided one bears in mind that confusing alterations of the form of the electrocardiogram are brought about by changes in the position of the heart (Chap 52) and by such extracardiac factors as emphysema and edema of the chest wall

Auricular hypertrophy is not detectable by physical examination and can only be suspected by fluoroscopy Broad and split P waves in bipolar electrocardiographic leads (usually associated with biphasic P waves in right sided chest leads) may be the only direct guide to left auricular hypertrophy (mitral P waves) Right auricular enlargement may be associated with tall narrow P waves

The x ray may at times yield useful information concerning hypertrophy of the various chambers but it is more apt to be valuable when dilatation coexists In many instances of right ventricular hypertrophy the x ray and the electrocardiogram reveal what appears to be a normal sized heart

the atrioventricular valves This is presumed to occur in impending or existent ventricular failure because under these circumstances the auriculo-*ventricular pressure gradient* is higher than normal at the onset of ventricular filling and the sudden equalization of pressure produces the changes in tension of the cusps When this occurs in early ventricular filling shortly after the atrioventricular valves *open* a *protodiastolic* gallop is produced when this occurs late in diastole as a result of auricular contraction a presystolic gallop ensues According to a second view the sound is not valvular in origin but is due rather to the impact of the increased early or late ventricular filling wave against the chest wall The adherents of this hypothesis believe that alterations in the ventricular wall as a result of failure permit the transmission of the impact of ventricular filling wave through the ventricles to contiguous structures A third view ascribes the gallop sound to sudden tensing of the pericardium as the dilated heart fills

The gallop is an important phenomenon because *it indicates* that the heart is dilated and that heart failure *if not present* is imminent The peculiar significance of the gallop is therefore that *this is the only physical sign to be elicited on examining* the heart which signifies that heart failure is either present or likely to occur All the other manifestations of heart failure tend to be elicited on examining other parts of the body

Aside from isolated presystolic and protodiastolic gallops one may have a summation gallop which occurs when the heart is dilated and the rate is rapid and since atrial contraction takes place very soon after the early rapid filling phase of diastole the two sounds are superimposed

Other types of three sound rhythm are less common and although in a given patient the recognition of the type may be of great practical importance space does not permit a detailed discussion The more salient points of the three sound rhythms are summarized in Table 109

HEART MURMURS

The rapid advances in cardiac surgery have made the precise recognition of the type and severity of valvular lesions a matter of practical rather than academic significance The several valvular lesions are considered in the next chapter and the discussion here deals only with certain general principles in regard to the interpretation of murmurs

When a heart murmur is heard one wishes first to know whether it is of functional origin and completely innocent or due to a structural lesion of the heart For practical purposes all diastolic murmurs are to be considered of structural origin This applies even to those faint early diastolic blows which are heard only along the left sternal margin during forced expiration with the patient leaning forward and to those short apical rumbles heard only after exercise in the limited region of the apex thrust with the patient lying on the left side Even when the usual causes aortic insufficiency and mitral stenosis are absent the diastolic murmurs still indicate organic disease of the heart. Some of the features which may aid in the detection of the less common causes of diastolic murmurs are summarized in Tables 110 and 111

The problem of the systolic murmur is more complex When such a murmur is loud (grade IV or more) or when it replaces the first sound at the apex or when it is associated with a genuine purring thrill it is of structural origin Even when these features are absent an apical systolic murmur should be considered significant if there is a diastolic murmur also or an opening snap The presence of a rheumatic history or of a very loud high pitched first sound makes it probable that an apical systolic murmur indicates mitral insufficiency Coexisting cardiac enlargement indicates that an apical systolic murmur is due to disease of the valve cusps to fibrosis of the annulus or to dilatation of the valve ring (relative mitral insufficiency)

At the aortic area faint systolic murmurs are common in patients with hypertension or dilatation of the aorta or syphilitic aortitis Even when such faint murmurs are transmitted to the carotid arteries they should not be considered as indicative of aortic stenosis unless accompanied by some of the other cardinal findings of this lesion Of these findings the faint or absent aortic second sound is the commonest while the thrill and the fluoroscopic demonstration of calcification of the aortic cusps are the most significant The plateau pulse is observed only when the lesion is far advanced When the systolic murmur is rough and loud at the aortic area these confirmatory signs are rarely needed However they are of importance when as occasionally happens the murmur is loudest at the left sternal margin or even at the apex.

Faint systolic murmurs at the pulmonary area are usually of functional origin and are especially common in individuals with anxiety states or with disorders accompanied by increased cardiac output Loud systolic murmurs along the left sternal margin are likely to indicate congenital malformation and especially an interventricular or interauricular shunt or pulmonic stenosis When the murmur at the pulmonary area is of moderate (grade III) intensity all these several possibilities must be considered and occasionally the differentiation of functional from congenital murmurs can be achieved only by cardiac catheterization Mitral stenosis and the other disorders which cause pulmonary hypertension (Chap 224) are also common causes of

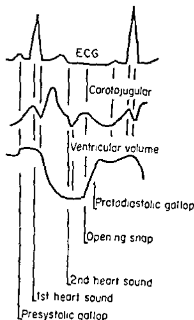


FIG 159 The *carotojugular* tracing represents the venous pulse during diastole with the characteristic waves During ejection the curve is of the arterial type The *ventricular volume* curve displays a small upstroke shortly after the onset of the P wave of the ECG The *presystolic gallop* occurs at this time During isometric contraction and isometric relaxation the ventricular volume curve is flat because blood is neither entering nor leaving the ventricle all valves being closed At the onset of the descent of the jugular V wave there is a sharp upstroke in the ventricular volume curve indicating rapid filling The opening snap of mitral stenosis occurs as ventricular filling begins The *protodiastolic gallop* occurs later toward the end of rapid filling

rise of ventricular pressure (3) the presence or absence of structural disease of the mitral valve and (4) the amount of tissue between the heart and the surface Loudness of the first sound is favored by short conduction time high cardiac output mitral stenosis and thinness the reverse of these conditions tends to be associated with faintness of the first sound

Aside from such extracardiac factors as obesity emphysema and effusions in the chest the intensity *and to some extent the quality of the second heart* sound may be influenced by alterations in the character of the vessel walls Accentuation of the aortic second sound is a normal phenomenon with age and occurs in such conditions as arteriosclerosis or syphilitic aortitis which may cause diffuse change in the physical properties of the wall of the aorta The other conditions which affect the intensity of the second sound are primarily those which alter the pressures in the aorta and pulmonary artery an increase in pressure tending to be associated with accentuation of the corresponding sounds

Three-sound Rhythms Under many different circumstances one hears upon listening to the heart not two sounds but three and the proper interpretation of the mechanisms and the significance of the extra sound will often prove to be of value in diagnosis The most common cause of a three sound rhythm in young persons is the presence of a normal third heart sound Here the additional sound is related to a change in tension in the auriculoventricular cusps as filling occurs

Almost equally as frequent as the physiologic third heart sound and of much greater practical significance is the gallop rhythm This term should be limited to a description of an extra sound occurring in diastole producing a cadence of sounds resembling that of a galloping horse (Fig 160) The protodiastolic gallop of a single cardiac cycle resembles the sequence when a physiologic third sound is present but the impression conveyed to the ear is quite different because the gallop usually occurs only in the presence of moderate to marked tachycardia and is not ordinarily observed with slow heart rates

Most gallops appear to arise in the left side of the heart as they are loudest during expiration and at the apex When a gallop is best heard during inspiration in the left parasternal region it is likely to be of right ventricular origin

The mechanism of the gallop rhythm is still a matter of dispute According to one view the sound is valvular in origin and is due to a wave of ventricular filling which causes a sudden tensing of



FIG 160 Presystolic and protodiastolic gallops After the P wave and shortly before the QRS begins a sound is noted This is the presystolic gallop and is related to ventricular filling induced by auricular contraction Approximately 0 12 sec after the beginning of the second heart sound there is an additional extra sound This is the protodiastolic gallop and occurs soon after auriculoventricular valves open and as the early rapid filling occurs

The gallop rhythms are so designated because the sound conveyed to the ear resembles that of a galloping horse

The gallop sounds are rarely heard except in the presence of tachycardia A three sound rhythm resembling during a single cycle the protodiastolic gallop is heard in young individuals with normal slow hearts This is the physiologic third heart sound However the cadence is not that of a gallop because the characteristic tachycardia is usually absent in such normal *persons*

Table 110 DIFFERENTIAL DIAGNOSIS OF THE MORE IMPORTANT CAUSES OF BASAL DIASTOLIC MURMURS

Origin and cause of murmur	Important points in history	Usual age of patient	Special features of murmur	Cardiac enlargement	Peripheral vascular signs	Important associated findings	Remarks
Rheumatic aortic regurgitation	Rheumatic fever	10–40	Early diastolic blowing Faint or loud	Left ventricular type	Regurgitation or stenosis	Mitral stenosis auricular fibrillation	Signs frequently modified by coexisting aortic stenosis and mitral lesions
Syphilitic aortic regurgitation	Syphilis	35–60	Blowing early diastolic often loud	Left ventricular type	Regurgitation	Positive serologic tests in about 85 per cent	Especially middle-aged Negro males aorta usually dilated (x-ray) Confusing systolic murmurs common
Hypertension		40+	Very faint	Left ventricular type	Absent	Hypertension (diastolic)	Regurgitation slight
Calcific aortic disease	Syncope Angina pectoris	55+	Diastolic faint systolic loud with systolic thrill	Left ventricular type	Stenosis	Calcification of aorta and aortic valves (x-ray)	Signs of stenosis predominate
Bacterial endocarditis	Rheumatic fever or murmur at birth	Any	Often intermittent	Left ventricular type	Regurgitation or stenosis	Fever positive blood culture Emboli Petechiae Hematuria	Usually superimposed on rheumatic lesion rarely on syphilitic or congenital bicuspid aortic valve
Bicuspid aortic valve		10–40	Faint			Liable to bacterial endocarditis	Usually associated with coarctation of aorta
Dissecting aneurysm	Sudden violent pain	35+	Often intermittent	Non left ventricular	Asymmetry in blood pressure	Hypertension	Cardiac tamponade from rupture into pericardium
Pulmonic regurgitation: Graham Steell murmur	Rheumatic fever or cor pulmonale	10–40	Faint, early blowing	Right ventricular type	Pulmonic second increased	Mitral stenosis or cor pulmonale	Impossible to distinguish from minimal aortic regurgitation
Pulmonic regurgitation: Overacting heart	Palpitation	Any	Faint early blowing		Bounding pulse	Anemia hyperthyroidism	Diastolic murmurs rare and faint systolic common and loud
Pulmonic regurgitation: Congenital lesions	See discussions of patent ductus arteriosus Eisenmenger complex, and Lutembacher syndrome						

occasional instance of asymptomatic minimal mitral insufficiency than to induce unnecessary alarm and anxiety

The Late Systolic Murmur Elderly persons may display faint or moderate murmurs which are loudest in the region of the apex, are often somewhat harsh begin in midsystole and last until the second heart sound. They may have a crescendo quality and this may lead to an erroneous diagnosis of mitral stenosis These late systolic murmurs are unique in that they are separated from the first sound by a distinct pause

The mechanism of these murmurs is unknown Some of the patients present evidence of cardiac failure without obvious cause and hence are considered to have senile heart disease (presbycardia) Others display the characteristic anginal pain of coronary disease or electrocardiographic changes pointing toward a previous myocardial infarction Necropsy has revealed fibrosis of the mitral annulus in some instances but in others has failed to furnish an adequate explanation for the murmur Auriculoventricular block of the higher grades is not infrequent in elderly patients with such murmurs

In younger persons these late systolic murmurs are rare They appear to be of extracardiac origin in some individuals and due to rheumatic disease of the mitral valve in others

Heart murmurs in patients with congenital heart disease are discussed in Chap 225

Thrills In the region of the apex thrills are of limited diagnostic import because they may be confused with vibrations set up by a vigorously beating heart On the other hand the presence of a thrill at the base of the heart or along the left sternal border constitutes practically *conclusive evi*

Table 109 DIFFERENTIAL DIAGNOSIS OF THE MORE COMMON CAUSES OF THREE SOUND RHYTHMS AT THE APEX *

Condition	Time of cardiac cycle	Third sound ventricular volume curve	Associated conditions	Significance of sound	Probable mechanism	Remarks
Physiologic third sound	Early diastole	Rapid filling	Good health	None	Change in tension of cusps with filling	Slow rate no gallop cadence low pitch
Protodiastolic gallop	Early diastole	Rapid filling phase	Failing heart	Failure present or imminent	Rapid equalization of pressure between auricle and ventricle	Tachycardia gallop cadence
Presystolic gallop	Presystolic	Atrial contraction	Failing heart	Failure present or imminent	Rapid equalization of pressure between auricle and ventricle	Tachycardia gallop cadence
Reduplicated first sound	Onset of systole	Preejection phase	Good health	None	Asynchronism of ventricles?	
Opening click	Early diastole	Onset of rapid filling phase	Early mitral stenosis	Indicates mitral stenosis	Rigidity of mitral cusps?	Synchronous with onset of descending limb of V wave in jugular pulse high pitch
Short early diastolic rumble	Early diastole	Rapid filling phase	Mitral stenosis auricular fibrillation	Indicates mitral stenosis	Obstruction at mitral orifice	A murmur of short duration
Audible atrial contraction	Diastole	Rapid filling phase or diastasis	Fibrosis of mitral annulus coronary sclerosis	Indicates heart block	Auricular systole	Rate usually very low
Premature beat causing single sound	Early in rapid filling				Beat very premature filling not adequate to develop enough energy to open semilunar valves hence no second sound	

In addition to the above intracardiac causes of three-sound rhythms there are several extracardiac causes including mediastinal emphysema pneumothorax air in the stomach and various unknown causes

moderate or faint pulmonary systolic murmurs as well as functional pulmonary diastolic blows (Graham Steell)

In most patients it is possible to arrive at a definitive and correct interpretation of the cause and significance of systolic murmurs However occasionally there will be doubt about a patient even after exhaustive study If there is no other evidence of cardiac disease the basal systolic murmur should be dismissed as of no significance and the patient should be emphatically reassured In the case of the apical systolic murmur it is perhaps wise to institute the proper prophylactic measures against bacterial endocarditis and against rheumatic fever and at the same time to stress the inconsequence of the murmur It is better to overlook an

Premature Beat Premature beats may arise in the atrium the junctional tissues or—much more frequently—in the ventricle (Chap 52) They are relatively more common in patients with structural cardiac disease than in healthy persons but since they are not rare in the healthy their presence has no diagnostic significance Occurring in the absence of organic heart disease premature beats may be due to emotional stress or the excessive use of tobacco coffee or tea In some instances they appear to result reflexly from distention of the stomach In many instances the cause cannot be determined The premature beat is usually recognized with ease because it consists of a contraction appearing before the next beat would ordinarily occur and is usually followed by a pause longer than the usual interval As a rule the patient is conscious of the premature beat (Chap 13) less frequently he notices the large beat after the compensatory pause

At times premature beats may occur in groups one after the other and under such circumstances the condition may be confused with auricular fibrillation an error which can be avoided by noting that the rhythm becomes regular when the heart is accelerated by exercise

One special type of premature beat merits additional comment This is *bigeminal rhythm* a state in which every alternate beat is premature This condition is usually the result of overdosage with digitalis and disappears within a few days after the drug has been withheld It should not be confused with *pulsus alternans* a disorder of rhythm in which every alternate beat is feeble but in which the rhythm remains regular In the case of both these disturbances one notes on taking the blood pressure that every alternate beat comes through at a lower level than the previous one (Chap 52) However on listening to the heart the irregularity is readily detected in the case of the bigeminal rhythm while no irregularity is noted in the case of pulsus alternans The *paradoxic pulse* which is sometimes confused with alternation or bigeminy will be discussed in the section dealing with pericarditis (p 1280)

The treatment of premature beats depends on the associated findings When they occur only occasionally and evidence of cardiac disease is lacking no treatment is needed When there exists a reasonable suspicion that tobacco or caffeine is the cause they should be withheld temporarily In excitable patients premature beats may disappear following the administration of mild sedatives The *Rauwolfia* derivatives and the other new tranquilizing drugs are often better than the barbiturates in such patients When premature beats occur in a person receiving full doses of digitalis the drug should be withdrawn for a few days if the irregularity is the result of digitalis it will then disappear In a fully digitalized patient the ingestion of a high carbohydrate meal may precipitate premature beats This is apparently related to hypopotassemia for potassium chloride (3 to 6 Gm daily in divided doses) will often abolish the arrhythmia in such persons In patients with cardiac failure digitalis in therapeutic doses may abolish premature beats Quinidine in doses of 0 1 to 0 2 Gm (1 5 to 3 gr) is a highly effective remedy for premature beats in some patients but should be given only when the extrasystoles are sufficiently frequent to cause an important mechanical inefficiency of the heart Procaine amide (Pronestyl) in doses of 250 to 500 mg orally two to four times daily is sometimes more effective than quinidine Atropine may eliminate premature beats in persons who have them only after meals

Auricular Fibrillation In the past this irregularity has been considered generally to be due to a circus movement—that is to say a wave of excitation circulating continuously in a short and irregular path about the mouths of the venae cavae (Chap 52) The irritable focus concept supported by Scherf and strongly substantiated by the thorough cinematographic studies of Prinzmetal and his colleagues is now becoming widely accepted The idea that premature beats and paroxysmal tachycardia are due to an irritable focus while auricular fibrillation and auricular flutter are dependent on a circus movement cannot be readily reconciled with the clinical facts Thus the same patient may exhibit all these different auricular arrhythmias within a few minutes Such instances support a unitary concept for the origin of all the auricular arrhythmias Some believe that auricular fibrillation may be caused either by a circus movement or by an irritable focus

Whichever may ultimately be proved to be the underlying mechanism of auricular fibrillation the effect is to obliterate the effective contraction of the atria and to bombard the atrioventricular node and the ventricles with a very rapid and irregular series of impulses Many of these impulses are blocked at the AV node but many pass through so that the ventricular contractions in the untreated patient are usually rapid and completely irregular (Chap 52)

When the rate is rapid—i e 120 or more—the diagnosis is made readily because auricular fibrillation is the only common condition in which one has the combination of a well marked tachycardia with a gross irregularity When the rate is normal or only slightly rapid as in digitalized patients the diagnosis is less readily apparent but the lack of any dominant rhythm or of any rhythmic pattern can usually be demonstrated by simultaneously listening to the heart and flexing one s finger with each beat in an attempt to determine whether there

Table 111 DIFFERENTIAL DIAGNOSIS OF THE MORE IMPORTANT APICAL DIASTOLIC MURMURS

Origin and cause of murmurs			Important points in history	Special feature of murmur	Cardiac enlargement	Important associated findings	Remarks
Murmurs arising at mitral orifice	With structural mitral disease	Mitral stenosis *	Rheumatic fever Chorea	Presystolic (regular rhythm) or early diastolic (auricular fibrillation)	Right ventricular type	Loud pulmonic second Loud first sound Systolic murmur	Very faint to moderately loud rumbling (see text) Compression of esophagus by left atrium (x ray)
		Congenital defects	Murmur since birth	Presystolic rumbling	Right ventricular type Marked enlargement of pulmonary artery (x ray)	Hilar dance (fluoroscopy)	Lutembacher's syndrome (septal defect and relative stenosis of tricuspid or mitral valve)
		Rytand's murmur	Syncopal attacks	Blowing faint often mid diastolic	Moderate to marked	Systolic murmur Heart block	Thickening or calcification of mitral annulus in elderly subjects
	Without structural mitral disease	Myxoma of left auricle	Embolism Syncope	Presystolic	Bizarre shape of auricle		Rapidly progressive heart failure
		Austin Flint murmur	Syphilis or rheumatic fever	Apical sharply localized	Left ventricular type	Outspoken signs of aortic regurgitation	Rough Presystolic no compression of esophagus by left atrium (x ray)
		Overactive heart	Palpitation	Presystolic	Slight or absent	Loud sounds systolic murmurs bounding pulse	Anemia or thyrotoxicosis (presystolic gallop resembling presystolic murmur)
Murmurs transmitted from other sites		From aortic valve	Rheumatic fever or syphilis	Loudest at base	Left ventricular type	Signs of aortic insufficiency	Blowing early diastolic
		From patent ductus arteriosus	Present since birth	Loudest at left second interspace	Enlarged pulmonary artery (x ray)	Bounding pulse High pulse pressure	Rough continuous with systolic intensification

* Mitral insufficiency with little or no stenosis may occasionally cause an apical diastolic rumble apparently due to increased flow through the mitral orifice

dence that the accompanying murmur is of the organic type It is true that thrills are simply the tactile equivalent of the auditory basis of the murmur and hence have no greater significance than the murmur itself It happens however that the kind of murmur that gives rise to vibrations that can be felt as a thrill are almost invariably of organic origin Such thrills are of especial importance in the diagnosis of aortic stenosis

DISTURBANCES OF RHYTHM AND RATE OF THE HEART

Certain disorders of the heart action are of importance because they may be responsible for serious consequences congestive failure angina pectoris or even death Others such as many of the irregularities are important because the anxiety they produce is commonly out of all proportion to their seriousness In exceptional instances the decision as to the type of irregularity has to be made by the electrocardiographic method which should be employed in all doubtful cases However the physician who has taken the time to study the arrhythmias carefully and who for a number of years has regularly correlated his clinical observations with electrocardiographic records can usually recognize the cardiac irregularities by simple auscultation

Some of the arrhythmias and especially premature beats tend to be precipitated by potassium deficiency which may be due to inadequate diet diuretic drugs or hormonal therapy

Disturbances of rhythm may be conveniently divided into two groups those which are very common and those which are less common The former group includes the sinus arrhythmia the premature beat and auricular fibrillation

Sinus Arrhythmia *Sinus arrhythmia is observed* in most healthy young persons and consists of quickening of the heart during inspiration and slowing during expiration It tends to be intensified by deep breathing and to disappear when the breath is held or when the heart rate is increased by exercise This arrhythmia has no significance

Premature Beat Premature beats may arise in the atrium the junctional tissues or—much more frequently—in the ventricle (Chap 52) They are relatively more common in patients with structural cardiac disease than in healthy persons but since they are not rare in the healthy their presence has no diagnostic significance Occurring in the absence of organic heart disease premature beats may be due to emotional stress or the excessive use of tobacco coffee or tea In some instances they appear to result reflexly from distention of the stomach In many instances the cause cannot be determined The premature beat is usually recognized with ease because it consists of a contraction appearing before the next beat would ordinarily occur and is usually followed by a pause longer than the usual interval As a rule the patient is conscious of the premature beat (Chap 13) less frequently he notices the large beat after the compensatory pause

At times premature beats may occur in groups one after the other and under such circumstances the condition may be confused with auricular fibrillation an error which can be avoided by noting that the rhythm becomes regular when the heart is accelerated by exercise

One special type of premature beat merits additional comment This is *bigeminal rhythm* a state in which every alternate beat is premature This condition is usually the result of overdosage with digitalis and disappears within a few days after the drug has been withheld It should not be confused with *pulsus alternans* a disorder of rhythm in which every alternate beat is feeble but in which the rhythm remains regular In the case of both these disturbances one notes on taking the blood pressure that every alternate beat comes through at a lower level than the previous one (Chap 52) However on listening to the heart, the irregularity is readily detected in the case of the bigeminal rhythm while no irregularity is noted in the case of pulsus alternans The *paradoxic pulse* which is sometimes confused with alternation or bigeminy will be discussed in the section dealing with pericarditis (p 1280)

The treatment of premature beats depends on the associated findings When they occur only occasionally and evidence of cardiac disease is lacking no treatment is needed When there exists a reasonable suspicion that tobacco or caffeine is the cause they should be withheld temporarily In excitable patients premature beats may disappear following the administration of mild sedatives The *Rauwolfia* derivatives and the other new tranquilizing drugs are often better than the barbiturates in such patients When premature beats occur in a person receiving full doses of digitalis the drug hould be withdrawn for a few days if the irregularity is the result of digitalis it will then disappear In a fully digitalized patient the ingestion of a high carbohydrate meal may precipitate premature beats This is apparently related to hypopotassemia for potassium chloride (3 to 6 Gm daily in divided doses) will often abolish the arrhythmia in such persons In patients with cardiac failure digitalis in therapeutic doses may abolish premature beats Quinidine in doses of 0 1 to 0 2 Gm (1.5 to 3 gr) is a highly effective remedy for premature beats in some patients but should be given only when the extrasystoles are sufficiently frequent to cause an important mechanical inefficiency of the heart Procaine amide (Pronestyl) in doses of 250 to 500 mg orally two to four times daily is sometimes more effective than quinidine Atropine may eliminate premature beats in persons who have them only after meals

Auricular Fibrillation In the past this irregularity has been considered generally to be due to a circus movement—that is to say a wave of excitation circulating continuously in a short and irregular path about the mouths of the venae cavae (Chap 52) The irritable focus concept supported by Scherf and strongly substantiated by the thorough cinematographic studies of Prinzmetal and his colleagues is now becoming widely accepted The idea that premature beats and paroxysmal tachycardia are due to an irritable focus while auricular fibrillation and auricular flutter are dependent on a circus movement cannot be readily reconciled with the clinical facts Thus the same patient may exhibit all these different auricular arrhythmias within a few minutes Such instances support a unitary concept for the origin of all the auricular arrhythmias Some believe that auricular fibrillation may be caused either by a circus movement or by an irritable focus

Whichever may ultimately be proved to be the underlying mechanism of auricular fibrillation the effect is to obliterate the effective contraction of the atria and to bombard the atrioventricular node and the ventricles with a very rapid and irregular series of impulses Many of these impulses are blocked at the AV node but many pass through so that the ventricular contractions in the untreated patient are usually rapid and completely irregular (Chap 52)

When the rate is rapid—i e 120 or more—the diagnosis is made readily because auricular fibrillation is the only common condition in which one has the combination of a well marked tachycardia with a gross irregularity When the rate is normal or only slightly rapid as in digitalized patients the diagnosis is less readily apparent but the lack of any dominant rhythm or of any rhythmic pattern can usually be demonstrated by simultaneously listening to the heart and flexing one s finger with each beat in an attempt to determine whether there

is predictability to the rhythm The distinction from numerous extrasystoles can be made by noting that while in both conditions one has beats of normal interval followed by groups of beats occurring at shorter intervals it is only in auricular fibrillation that abnormally long pauses will be noted to occur in groups of two or more More difficult and frequently impossible is the distinction of auricular fibrillation from auricular flutter with varying block and from "shifting pacemaker" in which there are auricular ectopic beats arising from multiple foci Both these conditions may produce total irregularity However since auricular fibrillation is very common while the other conditions are rare it is a safe rule to consider a person with a total irregularity in which the rhythm has no pattern and no predictability as having auricular fibrillation

Auricular fibrillation may be paroxysmal or persistent Occasionally the paroxysmal form occurs in healthy persons in whom no evidence of structural cardiac disease can be found It is also encountered in individuals who otherwise normal suffer from acute infectious diseases such as acute lobar pneumonia or in patients who are in the midst of acute illnesses primarily affecting the heart such as acute rheumatic carditis and acute myocardial infarction Rarely paroxysmal auricular fibrillation may be the consequence of anesthesia potassium deficiency digitalis intoxication or other forms of poisoning Most frequently however paroxysmal auricular fibrillation is seen in thyrotoxicosis in rheumatic heart disease with mitral stenosis or in senile heart disease In the latter two conditions the paroxysmal form not uncommonly occurs from time to time before the arrhythmia becomes permanently established The paroxysms are of variable duration lasting from a few seconds to a few days These attacks have the characteristics of all types of paroxysmal rapid heart action the onset and offset being sudden and unless the patient is observed in the midst of the attack the recognition of the nature of the episode will depend largely on the observation by the patient that the heart action is highly irregular during the attack

The permanent form of auricular fibrillation is confined almost exclusively to patients with senile heart disease mitral stenosis or thyrotoxicosis In elderly patients the usual signs of thyrotoxicosis may be absent and the presence of auricular fibrillation may be the only feature directing attention toward thyroid disease Rarely chronic auricular fibrillation may be the sole cause of congestive failure and in such instances reversion to normal rhythm is a curative procedure

The untoward effects of auricular fibrillation depend on the rapidity of the ventricular rate and the extent of the pulse deficit (i e on the proportion of ineffective and hence wasted ventricular beats) on the prior state of the affected heart on the duration of the attack and on the virtual paralysis of auricular contraction In the paroxysmal attacks the symptoms are identical with those observed in other forms of paroxysmal rapid heart action palpitation weakness dyspnea and in some cases congestive failure or prolonged anginal pain depending on the cardiac reserve or the efficiency of the coronary circulation In the chronic untreated cases the symptoms are essentially the same In cases brought under effective control by full doses of digitalis the symptoms disappear and the irregularity in itself has practically no harmful effect on the efficiency of the heart However in all cases—paroxysmal or permanent treated or untreated—the absence of atrial contractions favors the development of mural thrombi in the atria and exposes the patient to the hazards of embolism either in the lungs or in one or another of the systemic arterial branches

It is important to emphasize that when the ventricular rate fails to slow in the usual fashion in response to full therapeutic doses of digitalis the presence of thyrotoxicosis acute rheumatic carditis or pulmonary infarction should be suspected

In a patient with auricular fibrillation one faces the choice between two plans of therapy that of attempting to control the rate with digitalis the rhythm remaining irregular and that of abolishing the arrhythmia by the use of quinidine In patients with mitral stenosis quinidine is rarely effective in permanently restoring regular rhythm and appears to be especially hazardous The drug should be given with caution to patients with marked cardiac enlargement or long standing congestive failure although such patients occasionally are dramatically improved following restoration of the normal rhythm Quinidine is contraindicated when there is marked impairment of atrioventricular or intraventricular conduction because under such circumstances it may lead to fatal standstill or fibrillation of the ventricles Hence *quinidine is likely to be of greatest value in patients with recent auricular fibrillation* who are known to have had no evidences of congestive failure prior to the onset of the arrhythmia The initial dose of the drug should be small (0 1 to 0 2 Gm) and followed by a wait of several hours in order to make certain that the patient is not hypersensitive to it (as evidenced by respiratory difficulty syncope purpura) Quinidine may then be given in a dose of 0 4 Gm at 2 hr intervals for a total of five doses Conversion to normal sinus rhythm may occur while the quinidine is being administered or as is not infrequently the case may take place a number of hours after the last dose If the ectopic rhythm has not been abolished by the following morning 0 4 to 0 6 Gm (depending on the urgency of the problem) is again

given at intervals of 2 hr for five doses Only rarely will a larger dose be successful when the foregoing schedule has failed The treatment should be controlled with electrocardiograms before the third fourth and fifth doses when 0 4 Gm is administered although rarely does one encounter toxic effects for this dose If 0 6 Gm or larger amounts is given electrocardiograms should be taken just before each dose is to be given If the duration of the QRS complex or of the Q T interval has increased by 25 per cent or more or if a significant alteration in the form of the QRS has developed and *particularly if ventricular premature beats not previously present appear* quinidine should be discontinued at once It is unnecessary to control quinidine therapy by blood level estimations since so frequently conversion to normal rhythm takes place hours after maximal level has been reached and while the concentration in the blood is rapidly diminishing Quinidine should be given orally although if nausea and vomiting from one cause or another interfere with the taking of the drug preparations for intramuscular administration are available

Dangerous arrhythmias such as ventricular standstill or ventricular tachycardia may occur during quinidine therapy and manifest themselves only as brief syncopal seizures Such attacks appearing for the first time in a patient receiving quinidine make it imperative that the drug be discontinued in order to avoid a fatal termination

When the rhythm has reverted to normal maintenance doses of quinidine may be required in some patients although frequently the normal mechanism persists despite the discontinuance of quinidine

Procaine amide 0.25 to 0 5 Gm may be used in place of quinidine subject to the same precautions The two drugs may be combined but it has not been demonstrated that the combination is more effective or less toxic than either alone

The onset of auricular fibrillation in a patient who has repeatedly received mercurial diuretics or who has had prolonged anorexia may be a manifestation of potassium depletion and an indication for potassium chloride therapy

One point needs emphasis Although there are many instances of transient auricular fibrillation in which the administration of digitalis is followed shortly by the disappearance of the arrhythmia when auricular fibrillation is of long duration digitalis only rarely abolishes the arrhythmia Following the administration of this drug the atria usually continue to fibrillate However the ventricular rate diminishes strikingly and as the rate becomes slower the rhythm becomes less obviously irregular although careful observation supported by electrocardiographic tracings reveals that the ventricular irregularity does actually persist In some cases digitalis may cause a complete block at the AV node following which a regular ventricular rhythm may be seen but even here the atria continue to fibrillate

Thromboembolism is common in patients with chronic auricular fibrillation and is especially frequent in patients who also have mitral stenosis This complication is responsible for about 20 per cent of the deaths of such patients In order to prevent such episodes long term anticoagulant therapy has been advocated This is especially important in patients who have already experienced one or more thromboembolic episodes

The Less Common Arrhythmias These include the several types of heart block and the ectopic tachycardias other than auricular fibrillation

Heart Block The term *heart block* refers to a condition in which there is impairment of conduction from the atria to the ventricles through the AV node and main bundle *First degree block* is that state in which all the atrial beats are followed by ventricular beats but in which the duration of time for the passage of the impulse from the atria through the AV node and main bundle to the ventricles (P R interval) is prolonged *Second degree block* refers to a more advanced disturbance in the conduction system in which atrial impulses are from time to time incapable of penetrating the conduction system and exciting the ventricle *Third degree* or *complete heart block* describes the condition in which the conduction system is so altered that no atrial impulses reach the ventricles and the atria and ventricles beat independently at their own rhythms

FIRST DEGREE BLOCK (SIMPLE INCREASED P R INTERVAL) First degree block may be due to increased vagal tone in a perfectly normal individual or to fatigue in the conduction system as a result of prolonged tachycardia the action of digitalis or any of the inflammatory toxic degenerative or vascular processes that may affect the heart First degree block is an electrocardiographic diagnosis and produces no characteristic symptoms It may be suspected when a person suffering from rheumatic fever develops a sudden decline in the intensity of the first heart sound without any other change in the clinical picture and without evidence of fluid in the pericardium Another circumstance under which first degree heart block may be suspected clinically is when in the absence of auricular fibrillation a presystolic murmur becomes mid diastolic and ceases prior to the first heart sound First degree heart block requires no treatment the management being that of the underlying condition

It is generally considered that a P R interval greater than 0 20 to 0.21 sec represents first degree heart block and such a prolonged P R interval is held by some investigators to be evidence of myocardial disease However it is not uncommon to

and this is usually perceived by the patient The offset is likewise instantaneous but the sudden cessation of the ectopic rhythm is frequently not apparent to the patient However a story of instantaneous onset or offset if accurate allows one to know immediately that the attack represents an ectopic tachycardia of some type When the rate is less than 140 per minute the chances are *strong* that one is dealing with sinus tachycardia Rates of 170 and more per minute are almost invariably the result of ectopic rhythms and the difficulty comes chiefly in the group of patients with heart *rates between 140 and 170 When the rate is in* the general region of 150 ventricular and auricular tachycardias are unlikely and there is a distinct probability that if the rhythm is ectopic it is auricular flutter or nodal tachycardia

EXTREME SINUS TACHYCARDIA *The chief* causes of extreme sinus tachycardia are marked elevation of the body temperature severe thyrotoxicosis and any condition which produces profound circulatory collapse Occasionally acute myocardial injury due to infection infarction etc may be the cause but in most instances sinus tachycardia of severe degree is due to extracardiac causes Sinus tachycardia does not ordinarily respond significantly to carotid sinus pressure and in this respect resembles ventricular tachycardia When slowing does take place it is usually slight and neither slowing nor subsequent *acceleration* occurs with the abruptness observed in patients with auricular flutter In the absence of marked hyperthermia or severe thyrotoxicosis a patient with outspoken sinus tachycardia will usually display manifestations of forward failure (see Chap 14) *It should be emphasized* again that the differentiation between sinus and ectopic tachycardia is of the greatest practical importance because in the latter instance specific therapy aimed toward the heart may cause immediate benefit *Since sinus tachycardia requires no treatment* aside from that directed at its cause a word may be said regarding the use of digitalis in this condition Unless there are definite signs of congestive failure digitalis has no place in the treatment of sinus *tachycardia Not only is this* drug valueless under these circumstances but it may be dangerous Digitalis is not indicated merely because the heart rate is accelerated

ECTOPIC TACHYCARDIAS The most important of *these—auricular* fibrillation—has been considered already *Auricular flutter* is a much rarer but closely allied condition in which the circus movement follows a longer and more regular route or as newer observations suggest a condition fundamentally *identical* with paroxysmal auricular tachycardia differing only in that the irritable focus discharges at a much higher rate When the degree of block between atrium and *ventricle is variable* this disorder cannot be distinguished from auricular fibrillation with certainty except by the electrocardiographic method As a rule the atria beat at a rate of approximately 300 beats per minute and either 2 1 3 1 or 4 1 block exists the corresponding ventricular rates being about 150 100 or 75 When the block is constant and of high degree the condition *will usually not be suspected but if it is* suspected its presence can be confirmed by the fact that during exercise the heart rate increases suddenly rather than gradually and that in the postexercise period slowing occurs suddenly rather *than gradually In* an individual with sinus rhythm exercise causes increase in atrial rate in an individual with auricular flutter exercise has little effect on the atrial rate but the decrease in vagal tone tends to reduce the degree of block and since the *block* suddenly changes from the high degree to a lower degree the acceleration occurs in the space of a single heart beat More *commonly* with auricular flutter the ventricle responds to every alternate auricular impulse Under such circumstances the ventricular rate is usually between 140 and 160 and this fact alone should make one suspect the presence of flutter *because the other types of regular* tachycardia of ectopic origin are likely to be associated with faster rates When auricular flutter is suspected it will usually be found that carotid sinus pressure causes the ventricular rate to slow but that *the slowing is maintained only for the* brief period of the pressure and the heart then returns to the previous rate Furthermore both the deceleration and the acceleration occur instantly rather than gradually as would be the case with sinus tachycardia *if there were any response* at all to carotid sinus pressure

Occasionally the block is so variable that the high degree of ventricular irregularity is virtually identical with that observed in auricular fibrillation *The response to exercise may distinguish* the two arrhythmias in auricular flutter the irregularity may be abolished with the increased rate in auricular fibrillation the irregularity will be enhanced

Careful auscultation will frequently reveal an appreciable difference in the intensity of the first sound in auricular flutter due to slight variations in the timing of the ventricular contraction in response to the preceding atrial contraction *The principle* underlying this variability in the loudness of the first sound has been considered already This difference in the loudness of the first sound is never present in sinus tachycardia is rarely found in paroxys*mal auricular tachycardia and is frequently present* in ventricular tachycardia Hence while this sign is not specific for any one condition it can serve to limit the diagnostic possibilities when a tachycardia is first encountered

Auricular flutter is caused by essentially the same

conditions that cause auricular fibrillation has essentially the same prognostic significance and is treated in a somewhat similar manner Although the use of quinidine may occasionally cause auricular flutter to revert to normal rhythm such an effect is less likely than in the case of auricular fibrillation The usual method of treatment therefore is to administer digitalis which increases the degree of auriculoventricular block and commonly converts auricular flutter to auricular fibrillation When the drug is withdrawn such patients frequently will revert spontaneously to normal rhythm if this does not occur quinidine may be employed Occasionally it may be impossible to break up the abnormal auricular rhythm and in such an instance digitalis may be needed to maintain a degree of block sufficiently great to allow the heart rate to remain at relatively normal levels In an occasional patient digitalis will convert auricular flutter to sinus rhythm and will tend to prevent recurrences but this effect is unusual

Quinidine occasionally converts auricular fibrillation to auricular flutter Additional doses may then establish sinus rhythm or the flutter may persist The auricular rate may gradually decrease from approximately 300 to about 200 Under these circumstances the ventricular rate may suddenly increase the previous 2 1 ratio being replaced by a 1 1 ratio as the ventricle now responds to each auricular impulse When this occurs quinidine should be discontinued and digitalis administered even though this procedure may tend to cause re establishment of auricular fibrillation

When auricular flutter responds poorly to these methods of treatment and remains a serious threat because of persistent tachycardia beneficial effects may result from the administration of antithyroid drugs This procedure may also be beneficial in other types of ectopic tachycardia However the patient may have marked lassitude and other symptoms of hypothyroidism Hence antithyroid therapy should be reserved for patients who have evidence of thyrotoxicosis or if such evidence is lacking are refractory to the usual methods of treatment

Paroxysmal Auricular Tachycardia This is the most common of the ectopic tachycardias aside from auricular fibrillation (p 1241) It usually appears first in youth and attacks may continue to occur throughout life The majority of patients with this disorder display no evidence of any other cardiac abnormality *In such instances the attacks are never of serious consequence* unless they last for several days or longer However they usually produce great anxiety on the part of the patient and the family Any patient who has a history of recurrent attacks of rapid regular heart action setting in instantly and having been present since childhood or early adulthood and who displays no evidence of structural heart disease should be considered as having paroxysmal auricular tachycardia until the nature of the attacks can be established conclusively

When a patient is seen during an attack of auricular tachycardia the heart is found to be perfectly regular and the rate is usually 170 or faster Procedures which cause vagal stimulation either will have no effect or will cause the attack to cease abruptly Such procedures include pressure on the carotid sinus pressure on the eyeballs the induction of gagging or vomiting and attempted expiration with the glottis closed (the Valsalva experiment) When these several procedures attempted singly are unsuccessful they may still give a response when utilized in combination with one another

The causes of auricular tachycardia are unknown since most of the patients exhibit no signs of structural disease Prognosis as a rule is excellent even in untreated cases for the attacks tend to subside spontaneously after lasting for periods of minutes to hours Exceptionally the attacks may endure for several days and under such conditions fatigue of the heart muscle defective systolic discharge dilatation and congestive failure may supervene In the majority of the patients with this disorder the most serious aspect is the psychologic effect on the patient and on the family The attacks are alarming to them and many individuals subject to the disorder develop a secondary anxiety state which causes more suffering than the initiating disorder Hence the keystone of therapy in such a patient is proper reassurance coupled with attempts to prevent the seizures

For many patients digitalis is the most effective drug in preventing the attacks For other patients quinidine will be found to be more useful Certain patients notice that the attacks are regularly precipitated by certain trigger factors including anxiety physical fatigue abdominal distention the rapid ingestion of cold drinks and mild spontaneous hypoglycemia A careful history in regard to the exact precipitating circumstances will often enable the physician to ferret out these trigger factors and to instruct the patient how to avoid them

When a patient is seen during an attack of paroxysmal auricular tachycardia the following plan of procedure will be found effective in a considerable proportion of instances

1 Have the individual take a deep breath and attempt to expire against a closed glottis (the Valsalva maneuver)

2 Massage the carotid sinus region (first one side then the other) while listening to the heart discontinuing the massage if the rate slows abruptly

3 Carry out procedures (1) and (2) simultaneously

4 If the attack persists administer lanatoside C

(Cedilanid) 1 to 1 2 mg very slowly intravenously provided of course that the patient has not been receiving digitalis during the preceding 2 weeks

5 Repeat procedures (1) and (3) about 20 min after the injection

6 If the attack still persists neostigmine may be administered (0 5 mg) subcutaneously and the Valsalva maneuver and the carotid sinus pressure again repeated

7 Should the arrhythmia still persist the patient should be given morphine sulfate (10 to 15 mg) subcutaneously During the ensuing sleep the attack will usually cease

8 In desperate instances which are very exceptional with prolonged attacks Mecholyl may be administered in doses of 5 mg repeated every few minutes until the attack ceases or untoward symptoms develop However this drug is likely to produce alarming reactions and is rarely indicated Whenever it is employed a previously prepared solution of atropine sulfate (1 mg) should be available for use if serious toxic effects occur

The description above refers to management of attacks by the physician In addition the patient should be instructed to apply the Valsalva procedure, to utilize carotid sinus pressure to employ ocular pressure and to induce gagging and vomiting by inserting his finger into his pharynx In many instances patients learn to terminate their own attacks by these means

It should be emphasized that auricular tachycardia may produce well marked deformity of the QRS complex and this may lead to an erroneous diagnosis of ventricular tachycardia The QRS changes disappear quickly but the T wave changes may persist for several days after termination of the paroxysm and a mistaken diagnosis of myocardial infarction may be made Rarely auricular tachycardia may actually lead to myocardial infarction as the result of the diminished coronary flow resulting from the tachycardia and the increased energy expenditure of the heart

Paroxysmal Ventricular Tachycardia This is a rarer and much more serious disorder than paroxysmal auricular tachycardia The commonest cause is coronary disease and this arrhythmia frequently supervenes within a period of a few days following the development of a myocardial infarction Less commonly it is induced by the administration of digitalis in excessive amounts and very rarely the arrhythmia appears spontaneously in healthy individuals presenting no evidence of cardiac disease The diagnosis can usually be made without instrumental aid by the presence of several of the following clinical features (1) The patient commonly has evidence of coronary artery disease or has been receiving digitalis in rather large doses (2) As a rule there is no story of numerous previous attacks (3) During the attack the heart rate is usually between 160 and 210 and although it is essentially regular there may be slight variations in the regularity of the rhythm and in the intensity of the first sound from beat to beat because the relationship between atrial and ventricular contractions is somewhat variable (4) Carotid sinus stimulation has no effect on the rate

In doubtful cases electrocardiograms are necessary but even here the interpretation may be rendered difficult because auricular tachycardia which has endured for several hours often leads to conduction defects which cause the tracing to resemble that of ventricular tachycardia The electrocardiographic diagnosis cannot be made with certainty on the sole basis of the abnormal ventricular complexes In addition it is necessary that the P waves be shown to occur at a rate independent of the ventricular rate or that there be demonstrated in the intervals between attacks ventricular premature beats identical in form to the complexes seen during the paroxysm

Since it is but one step removed from the almost invariably fatal ventricular fibrillation ventricular tachycardia is the most serious of the ectopic tachycardias Fortunately quinidine is often very effective in the treatment of this condition The initial oral dose of quinidine should usually be 0 5 Gm and increasingly large doses should be given at intervals of 3 to 4 hr until the arrhythmia has broken or a dose of 1 0 Gm is given In most instances such dosage will suffice but occasionally larger doses are required

Procaine amide (Pronestyl) may also be effective in abolishing the attack and is probably safer than quinidine for intravenous use It may be administered as a slow drip in 5 per cent glucose at a rate of 500 mg per hr for 2 hr It is more effective if the patient has already received quinidine orally Either of these drugs may induce ventricular tachycardia or ventricular fibrillation They are contraindicated when these arrhythmias occur in patients with heart block (p 1243) When a patient is receiving these drugs in large dosage electrocardiograms should be made at hourly intervals Progressive widening of the QRS complex makes it likely that the drug is exerting a deleterious effect

Atropine combined with quinidine has occasionally been beneficial as have potassium chloride and magnesium sulfate

When heart failure occurs in an undigitalized patient with ventricular tachycardia digitalis should be administered The drug is not especially hazardous in such patients as was formerly believed

Nodal Tachycardia This condition is rare and is usually the result of digitalis therapy It may be suspected when an individual with a heart rate of 140 or more who has been receiving digitalis is

found to have a striking systolic pulsation in the jugular veins as the result of the simultaneous contraction of the atria and ventricles As a rule the diagnosis can be made only by electrocardiography The treatment is that of ventricular tachycardia

Clinical Picture The clinical picture presented by a patient during an attack of ectopic tachycardia varies with the age of the patient rapidity of the heart rate the duration of the attack the condition of the heart and the temperament of the patient In short attacks there may be experienced only a sense of fluttering in the chest or neck and a mild feeling of faintness the more stolid person may have no symptoms and remain unaware of the cardiac disturbance In longer attacks the characteristic features of forward failure appear more pronounced weakness and faintness the skin cool pallid and moist the systolic and the pulse pressures diminished Eventually—after days in a young normal person or after a few hours in an elderly person or in one already suffering from heart disease—congestive failure may supervene Angina may rarely appear in persons who have structurally normal hearts but it occurs more readily in those already suffering from impaired coronary circulation it is due to the increased energy expenditure of the myocardium and the reduction in coronary flow during the attack Occasionally fever may be present presumably owing in part at least to the disturbed dissipation of body heat and when this is associated with leukocytosis angina and T wave alterations of the coronary type (which may persist for some time following the cessation of the attack) confusion with myocardial infarction is possible

Some of the more important features of the ectopic tachycardias are summarized in Table 112

The value of electrocardiographic tracings in the differential diagnosis of the tachycardias is obvious Since registration of atrial activity is particularly desirable records should be obtained from the right of the sternum and in many instances while carotid sinus pressure is being applied At times the use of esophageal leads may demonstrate P waves which are not clearly seen in the conventional leads and thus clarify the nature of the arrhythmias

Harmful Effects of the Arrhythmias The physician will be much aided in management of patients presenting disturbances of the cardiac rhythm if he has a clear comprehension of the significance of such disorders When the heart rate is 28 to 30 or more the bradycardias produce certain changes in the circulation that have little or no clinical significance Owing to the large output of blood with each beat and the long diastolic pause the systolic ... ssure is elevated and the diastolic pressure is diminished The low average diastolic pressure tends to diminish coronary blood flow which occurs chiefly in diastole When the efficiency of the heart is otherwise unimpaired patients with this degree of bradycardia carry on a normal or practically normal existence When the heart rate slows to 15 or less the circulation to the brain becomes inadequate and Adams Stokes attacks occur or complete standstill or fibrillation of the ventricles leads to death

The tachycardias are important for a number of reasons Cardiac output and cerebral blood flow are diminished and although faintness is usually present actual unconsciousness rarely occurs unless the patient persists in maintaining the upright posture The tachycardias also cause marked interference with the coronary blood flow because most of the flow to the subendocardial part of the left ventricle takes place only during diastole Since the duration of systole is not much shortened with rapid heart rates the total amount of systole per minute is markedly increased and the total amount of diastole per minute is correspondingly reduced when the heart rate is excessively rapid Furthermore it should be remembered that the energy expended by the heart at each beat consists of two components of which one fraction—that used in raising the intraventricular pressure sufficiently to open the semilunar valves—is not used for the expulsion of blood At rapid heart rates the fraction of energy thereby wasted is correspondingly increased For these reasons tachycardia alone if sufficiently severe and prolonged may lead an otherwise healthy heart to fail

Aside from the deleterious effects of alterations in rate in either direction irregularity of the heart may itself be harmful This occurs when ectopic beats set in so early in diastole that the degree of ventricular filling is slight and the energy developed at the contraction is not sufficient to expel a significant amount of blood

ELECTROCARDIOGRAPHY IN RELATION TO DIAGNOSIS OF CARDIAC DISEASE

It is essential that every physician whether or not he has a primary interest in electocardiography or in diseases of the heart or even in the broader field of internal medicine have a general concept of the functions and limitations of electrocardiographic examination in the diagnosis and management of heart disease The late Frank N Wilson spoke of "the present wretched state of electrocardiographic diagnosis and the misery attributed to it In part this unfortunate situation is due to the lack of comprehension by many physicians of the kind of information electrocardiography can or cannot bring to them

In patients with arrhythmias the ECG usually

Table 112 THE MORE IMPORTANT CLINICAL FEATURES OF THE VARIOUS TYPES OF TACHYCARDIA

Condition	Common causes	Other etiologic data: Age at first attack	Other etiologic data: Heart disease	Usual heart rate	Rhythm	Effect of vagal stimulation*	Effect of digitalis	Effect of quinidine	Remarks
Sinus tachycardia	When moderate: exercise, emotion, almost any illness. When marked: hyperthermia, thyrotoxicosis, and circulatory failure	Any	Usually absent	100–160	Regular	No effect, or slight temporary slowing	None	None	Onset and end gradual (abrupt onset and end in all ectopic tachycardias)
Auricular fibrillation	Mitral stenosis, senile heart disease, thyrotoxicosis	Adults	Nearly always present	120–160 (slower when digitalized)	Totally irregular	Slight temporary slowing	Rate slowed; irregularity tends to persist †	Restores normal rhythm	The only common cause of tachycardia with gross irregularity
Auricular flutter	Mitral stenosis, senile heart disease, thyrotoxicosis	Adults	Nearly always present	About 150; 100 or 75 (with 2:1, 3:1 or 4:1 block)	Regular (rarely totally irregular)	Temporary abrupt slowing; abrupt return to rapid rate	May convert to auricular fibrillation	May restore normal rhythm	When rate is normal, exercise causes abrupt acceleration with later abrupt deceleration
Paroxysmal auricular tachycardia	Unknown	Childhood or young adulthood	Usually absent	160–220	Regular	Either no effect or abolition of attack	May relieve attack. Often prevents attacks	May relieve or prevent seizures	The only common cause of extreme tachycardia in a young adult without evidence of structural heart disease
Paroxysmal ventricular tachycardia	Coronary disease. Digitalis	Usually over 50	Nearly always present	160–220	Essentially regular with occasional slight irregularity	None	Indicated only if heart failure develops	Relieves and prevents seizures	May terminate fatally

* Including carotid sinus pressure, ocular pressure, holding breath, Valsalva experiment, induction of gagging, and induction of vomiting.
† Digitalis may abolish or prevent auricular fibrillation or flutter in some patients; this is exceptional.

yields precise information Alterations in P waves may furnish clues to the presence of mitral stenosis cor pulmonale or atrial septal defects but such clues need to be supplemented by other more decisive information

Abnormalities in the form of the ventricular complex are often erroneously evaluated There is strong evidence that the Q R S T sequence is mainly dependent on the subepicardial portions of the ventricle and that the subendocardial fibers are electrically silent Therefore subepicardial fibrosis due to such innocent causes as healed focal pericarditis or remote contusions of the heart (Fig 161) may cause impressive changes in the ECG while an extensive recent subendocardial infarction may show no significant change T waves are especially labile and may be altered by electrolyte shifts emotion tachycardia pressure on the ventricle ingestion of iced drinks or even by a carbohydrate rich meal (Fig 162) The QRS complex is less unstable and the presence of prominent Q waves in leads I or II or in the apical or left lateral precordial regions usually means focal disease of the myocardium However there is no necessary parallelism between such a change and the gravity of the clinical picture or even the nature of the underlying disease process It so happens that coronary disease is the commonest cause of focal myocardial disease but identical changes may be induced by other localized disorders such as abscess or tumor Thus except in patients with arrhythmias therapy should be based on the clinical picture Diagnosis is based on evaluation of *all* the evidence with emphasis in most instances on that derived from the clinical study

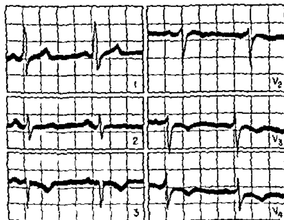


Fig 161 This 32 year-old man had been rejected for insurance because of the inverted T waves in the precordial leads These had been interpreted as evidence of coronary artery disease The history physical examination and fluoroscopic study revealed no evidence of cardiac disease The patient was able to perform vigorous and even violent exercise without any symptoms pointing toward cardiac disease

Four years previously his sternum had been fractured by impact against the steering wheel in an automobile accident The electrocardiographic changes illustrated are believed to have resulted from a contusion of the heart and are not considered to have any clinical significance The record illustrates the fallacy of placing predominant emphasis upon the electrocardiographic rather than on the clinical findings

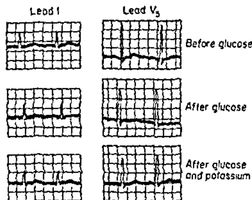


Fig 162 The patient is a healthy 44 year-old man without evidence of cardiovascular disease The T waves which were upright in the fasting state became inverted in V and isoelectric in lead I 40 min after the ingestion of 100 Gm glucose When KCl was administered with the glucose on the following day the T waves remained unchanged The record illustrates the fallacy of diagnosing coronary disease or any type of organic heart disease on the basis of T wave inversion alone

As Wilson and his coworkers stated

Electrocardiographic abnormalities are not diseases They have no important bearing upon the life expectancy of the patient or the extent to which his mode of life should be altered when there is a reasonable doubt as to the nature of the factor or factors responsible for them in that particular case

BALLISTOCARDIOGRAPHY

There is reason to believe that this method will ultimately be of great practical value because the records are related to the force of the heart beat Thus the ballistocardiogram tends to furnish an index to the quality of contraction which appears to be altered in many persons years before the quantity of contraction (output) is affected Pending further technical improvements and pending more complete knowledge of the mechanism of the various waves in normal persons the ballistocardiogram must be looked upon as a research method rather than a clinical procedure

The value of cardiac fluoroscopy has been indicated in the preceding pages

Other useful procedures in examining the heart include cardiac catheterization angiocardiography and oximetry Since these procedures are of particular value in the differential diagnosis of congenital heart disease they are discussed in Chap 225

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224 ETIOLOGIC ASPECTS OF HEART DISEASE (Including Treatment of the Different Types)

William H Resnik and
T R Harrison

RHEUMATIC HEART DISEASE

Rheumatic fever was first clearly separated from gout by Sydenham (1683) More than 100 years passed before Pitcairn (1788) Edward Jenner (1789) and Wells (1810) emphasized the relationship between rheumatic fever and the subsequent development of *cardiac disease This concept* was firmly established by Bouillaud (1834) It was not until 1904 that the specific pathologic lesion characteristic of the disease was described by Aschoff

In the United States rheumatic heart disease has now assumed first rank as a cause of death among children of school age and is second only to tuberculosis as a cause of death in young adults

Acute Rheumatic Carditis

Rheumatic heart disease refers either to the active form commonly designated as acute carditis in which acute inflammatory lesions are developing or regressing or to the inactive form in which the rheumatic process has spent itself and has left behind as a residue a permanently damaged heart The two forms may occur simultaneously when an acute exacerbation of rheumatic fever takes place in an individual who already has undergone permanent structural alteration in the heart as the result of past episodes of rheumatic fever

It is now generally accepted that involvement of the heart is an almost universal phenomenon of all cases of rheumatic fever If this view is correct the concern is not whether the heart has been affected in rheumatic fever for the decision is implicit in the diagnosis The more relevant question is how seriously the heart has been affected The grades may vary from the mildest subclinical forms in which minimal lesions are present which reveal no definite clinical signs that point specifically to cardiac involvement to the types in which extensive and severe pathologic changes in the heart are unmistakably manifested by abnormal clinical signs Through common usage the term *active carditis* is generally limited to those cases in which the clinical signs of impairment of the heart are more or less definite

The combination of fever acutely inflamed joints and pericarditis raises the question of differentiation between rheumatic fever with carditis and disseminated lupus When the characteristic skin lesions of lupus erythematosus are present and L E cells are demonstrated the problem is settled in their absence it is more difficult Leukopenia red blood cells in the urine splenomegaly and lymphadenopathy are practically decisive evidence in favor of lupus Rheumatic pericarditis is invariably a manifestation of severe pancarditis and is usually associated with loud murmurs and significant prolongation of the P R interval Evidence of pericarditis without signs of valvular or myocardial injury is frequent in patients with lupus In some instances the differentiation is possible only at a later date and depends on whether the characteristic valvular lesions of chronic rheumatic heart disease have developed

Management Since treatment of acute rheumatic fever and prevention of recurrence have already been discussed (p 867) the following remarks are confined to the problems peculiar to acute rheumatic carditis Salicylates are often strikingly beneficial in controlling acute rheumatic pericarditis but are otherwise ineffective Similarly digitalis is rarely of benefit in the treatment of congestive failure or auricular fibrillation when they occur during acute rheumatic carditis

The value of adrenocortical hormones in preventing the development of permanent cardiac damage is in doubt However there appears to be sufficient evidence that the incidence of residual valvular defects can be lessened provided large enough doses of the steroids or of ACTH are administered within the first 3 weeks after the onset ACTH gel 100 to 200 mg or cortisone 300 to 500 mg or prednisone 100 to 160 mg should be given daily in divided doses at 6- to 8 hr intervals Prednisone is probably preferable since it may be given orally and since it entails a lessened risk of fluid retention The usual precautions should be observed careful observation of the blood pressure and search for evidence of excessive salt and water retention restriction of sodium intake administration of potassium chloride 1 0 Gm three times daily and of an aluminum gel to diminish the danger of peptic ulcer formation Phenoxymethyl penicillin should also be given orally 0 3 Gm (500 000 units) four times daily to destroy any residual hemolytic streptococcus organisms and to prevent so far as possible other secondary infections that might arise as a result of the hormone treatment This regime should be continued for 6 weeks and then tapered off gradually

The question of the duration and rigidity of restriction of activity in patients with acute rheumatic carditis is difficult Ideally activity should be kept at a minimum until all traces of the rheumatic process have subsided and this means bed rest with possibly a few hours in a chair and bathroom privileges when fever and tachycardia approach normality Unfortunately there is no certain test that indicates the complete cessation of rheumatic activity Persistent elevation of the sedimentation rate of the C reactive protein or of the antistreptolysin titer when not accompanied by fever tachycardia or other chemical evidence of active injury is not an indication for rigid rest

After all signs of rheumatic activity disappear physical activity may be increased gradually during a period of 2 or 3 months with frequent evaluation of the clinical state If after such time no evidence of diminished cardiac reserve or of recrudescence of rheumatic carditis appears the patient may be allowed freedom to do as he pleases provided he lives below the symptom threshold i e does not incur dyspnea or fatigue

In an individual with chronic rheumatic heart disease who is under the age of thirty five the development of *congestive failure* constitutes presumptive evidence of recurrent activity and both

conditions should be treated Even in older patients with rheumatic heart disease the presence of digitalis resistant heart failure should arouse the suspicion of active rheumatic carditis

In younger children the necessity for long continued bed rest poses a difficult problem of psychologic management Prolonged absence from school deterioration of morale and the danger of developing a lifelong anxiety state are factors that require consideration and appropriate management

Chronic Rheumatic Valvular Heart Disease

The diagnosis of chronic rheumatic heart disease rests on the recognition of the various valvular lesions that are the invariable accompaniment of this disorder

General Comments The clinical course of rheumatic heart disease varies markedly in relation to the presence or absence of repeated or persistent activity of the rheumatic process At one extreme there is the child or young adult with persistent active infection and the development within a few months of evidence of myocardial pericardial and endocardial damage In such patients it is common to witness soon thereafter the appearance of intractable and progressive congestive heart failure and death within a year or two after the onset of the initial attack At the other extreme is the middle aged person in perfect health with or without a story of fever and joint pains in youth who is discovered to have a valvular lesion (most commonly mitral regurgitation but occasionally mitral stenosis or aortic valvular disease) but without any symptoms either at rest or upon strenuous effort In such individuals the minimal valvular damage has usually resulted from a single rheumatic episode The heart has adjusted to the mechanical defect and health may remain entirely unimpaired The patient may eventually die of some unrelated process or not rarely he may develop congestive failure after the age of sixty as senile myocardial degeneration sets in Between these two extremes there is every intermediate gradation

It is of importance to note that the patients with minimal valve lesions and without symptoms of congestive failure or diminished cardiac reserve are peculiarly susceptible to the development of bacterial endocarditis a complication which rarely occurs in the presence of lesions so far advanced as to cause congestive failure

The relation of auricular fibrillation to rheumatic heart disease is of interest This complication practically never occurs in patients with involvement of the aortic valve alone It is somewhat rare when mitral regurgitation without stenosis exists However it is very common in persons with long standing mitral stenosis and in such patients the onset of auricular fibrillation frequently converts a previously asymptomatic state into congestive failure Since digitalis produces striking benefit when it slows the rate even though the total irregularity persists it is clear that the harmful effects of the arrhythmia are in part the result of the tachycardia and of the pulse deficit rather than of the irregularity Nevertheless some patients are decidedly improved by conversion to regular rhythm (p 1242) Embolic phenomena appearing in patients with rheumatic heart disease may occur as the result of infected valvular thrombi when bacterial endocarditis coexists or as the result of sterile thrombi arising in the left atrium or its appendage in patients with mitral stenosis The likelihood of the development of atrial thrombi and consequent embolism is much greater in patients with auricular fibrillation than in those with regular rhythm The seriousness of embolism depends on the size and location of the occluded artery

Prognosis Prognosis depends on a multitude of factors The first of these is the persistence or recurrence of active rheumatic carditis The second is the cardiac reserve as indicated by the exercise tolerance The duration of life tends to be shorter after onset of symptoms in patients with aortic lesions who are particularly likely to encounter angina pectoris sudden death or rapidly progressive failure Obviously the prognosis is completely uncertain in patients who have angina pectoris The prognosis of subacute bacterial endocarditis is now usually good although many patients with this condition are unfortunately left with an exaggeration of the valve lesion Previous concepts of prognosis are constantly undergoing revision as the result of the rapid advances in valvular surgery

Aortic Stenosis Aside from the rather rare instances of congenital subaortic stenosis virtually all cases of aortic stenosis up to the age of fifty are due either to congenital malformations of the valve cusps or to previous rheumatic fever Some investigators hold that all cases below the age of thirty are on a congenital basis In both instances the valves may become so distorted and sometimes so densely calcified that it may be difficult to distinguish between the two

After the age of fifty five to sixty calcific aortic stenosis is far more common in men and its etiologic basis is uncertain When mitral stenosis is also present it is logical to assume that both lesions have the same rheumatic origin When aortic valve involvement alone is concerned it is generally believed that the lesion is primarily rheumatic with secondary deposition of calcium There are some grounds for holding that the lesion may be due solely to atherosclerotic distortion of the valves In rare cases identical lesions have been found in young persons with hypercholesteremic xanthoma

tosis who lack all stigmas of previous involvement by rheumatic fever Probably the strongest evidence is that persons of fifty five or older known to have been free of any sign of valvular disease in the immediately preceding years have been observed to develop aortic stenosis almost literally under one s stethoscope

Symptoms The symptoms especially characteristic of aortic stenosis are due to the obstructive lesion that leads to an increasingly fixed cardiac output and are due also to the striking hypertrophy of the left ventricular musculature *Syncope on exertion* occurs in 10 to 20 per cent of the cases and is probably due to inability of cardiac output to increase as peripheral resistance diminishes in response to muscular exertion This leads to a sudden fall in blood pressure cerebral hypoxia and loss of consciousness This symptom has grave prognostic significance since it implies a severe obstruction death usually occurs within 3 years The hypertrophy of the left ventricle and the tremendous increase in the work of this chamber outgrow the capacity of the coronaries to supply an adequate flow of blood to the myocardium and myocardial hypoxia ensues even when the coronaries are free of significant disease *Angina pectoris* develops in about one third the patients and rarely myocardial infarction may be seen even when the coronaries are relatively normal *Sudden death* occurs in about 20 to 25 per cent

Signs The classic signs of this disorder are the loud rough systolic murmur usually heard best in the second right interspace and well transmitted into the neck the corresponding thrill the diminished or absent second aortic sound the slowly rising pulse of low volume (plateau pulse) and the presence of calcification in the region of the aortic cusps as revealed by fluoroscopy However the signs vary considerably The murmur may be loudest over the body of the heart or at the apex and it may disappear completely during congestive failure reappearing when compensation has been restored The thrill not always present is usually proportional to the loudness of the murmur but there is no necessary parallelism between the latter and the severity of the stenosis The second sound over the aortic area is well heard in about half the cases in some cases because of residual pliancy of the cusps in others because of transmission of the second pulmonic sound The character of the pulse is dependent on the degree of stenosis and is so often modified by a coexistent regurgitation that it is not of great value in diagnosis The pulse pressure is diminished in some instances but is often normal or high because of aortic insufficiency or rigidity of the aorta Calcification of the valves is absent in over half the cases and its detection is dependent on the skill and experience of the fluoroscopist The left ventricular hypertrophy is indicated by the localized thrust at the apex x ray reveals the characteristic appearance of left ventricular enlargement The electrocardiogram displays left ventricular hypertrophy unless the stenosis is slight Frequently the coved T waves of myocardial hypoxia are encountered and when the R wave is absent in the first three precordial leads differentiation from an old healed septal infarct may be difficult or impossible

When the classic textbook" findings are elicited the diagnosis is not difficult However it is important to bear in mind that the departures from this idealized picture are frequent and that aortic stenosis is still often unsuspected until revealed at the autopsy table

When congestive failure appears the outlook is usually poor death commonly resulting from increasingly refractory heart failure in 2 or 3 years However this prognosis is subject to variation depending on whether the failure is due to the severity of the stenosis or to more remediable factors such as excessive exertion or salt ingestion Occasionally one encounters a person in the seventies or eighties known to have had the characteristic signs of aortic stenosis for years and who continues to remain completely asymptomatic

Treatment Treatment consists of the usual precautionary measures against the development of subacute bacterial endocarditis and of congestive failure or angina should they occur Surgical dilatation of the valve has been successfully employed although the mortality still remains high

Aortic Insufficiency Occasionally this defect may result from a congenital bicuspid valve usually in conjunction with coarctation of the aorta In practically all other instances up to the age of thirty the lesion is due to rheumatic fever In the thirties and forties the problem is usually one of differentiation of rheumatic from syphilitic aortic regurgitation and in the late fifties and beyond from atherosclerotic disease of the aortic valves In male patients aortic insufficiency may occur as an apparent complication of rheumatoid arthritis or rheumatoid spondylitis A history of rheumatic fever and the presence of mitral stenosis and of aortic stenosis before fifty are the chief points in favor of a rheumatic origin Rarer causes of the valvular defect are bacterial endocarditis the anatomic disruption of the valve being one of the chief causes of mortality in this condition even when the infection is eradicated injury to the valve by trauma distortion of the valve by dissecting aneurysm stretching of the aortic ring in severe hypertension producing a relative aortic regurgitation fenestration of the aortic cusps and medial necrosis with widening of the root of the aorta sometimes associated with arachnodactyly (Marfan s disease)

Symptoms Pure aortic regurgitation can cause hypoxia of the myocardium and hence angina and sudden death but this occurs far less frequently than in stenosis Usually rheumatic aortic insufficiency remains asymptomatic for a long period Once dyspnea on mild effort begins seizures of paroxysmal nocturnal dyspnea are common and from this point on congestive failure tends to supervene and to progress rapidly

Signs The high pitched blowing murmur heard best at the aortic area or along the left sternal border *is the cardinal sign of this lesion Sometimes* the murmur is so faint that it can be elicited only at the end of held expiration when the patient leans forward The Austin Flint murmur mimicking mitral stenosis is frequently heard The peripheral signs are also important the wide pulse pressure the *water hammer pulse the collapsing pulse the* pistol shot sound the double Duroziez murmur and the capillary pulse—all indicative of a leak from the arterial system and of a peripheral vasodilatation Not infrequently the presence of the peripheral signs may lead to the discovery of the diastolic murmur that may have been overlooked The x ray reveals the enlargement of the left ventricle and the electrocardiogram usually is that of left ventricular hypertrophy and "strain A more reliable manifestation of left ventricular hypertrophy is the localized apical thrust

Treatment Treatment is essentially the same as that of aortic stenosis Operative reduction of the leak has been successfully accomplished by insertion of the Hufnagel plastic valve but long range evaluation of this procedure is still needed

Mitral Stenosis In mild cases dyspnea on exertion due to the obstructive effect of the mitral lesion is the outstanding symptom As the lesion becomes more advanced two types of compensatory adjustment occur the clinical picture depends in large measure upon which predominates

Rise in pressure in the left auricle and in the pulmonary veins and capillaries tends to maintain the cardiac output but at the cost of enhancing the congestion of the lungs Thus dyspnea becomes increasingly disabling and paroxysmal dyspnea sometimes culminating in fatal pulmonary edema is an ever present threat whenever cardiac flow is increased by exertion or fever or whenever a paroxysmal tachycardia propels blood through the lungs into the left atrium faster than the blood can flow from this chamber into the ventricle Recurrent hemoptyses due to the development of anastomatic channels between pulmonary veins and bronchial veins are also common Right sided failure is absent or minimal Physical examination reveals the characteristic presystolic crescendo rumble culminating in the loud sharp first sound In addition there may be an early mitral murmur which may be brief or may fill the entire diastole fusing with the presystolic murmur The opening snap is common and the second pulmonic sound is only slightly accentuated Aside from the enlarged left auricle and the small aorta the x ray is essentially negative The electrocardiogram also is negative except for the broad notched P wave

The second method of adjustment is by *increase in pulmonary arteriolar resistance* As this takes place and becomes more severe the flow through the lungs and the cardiac output diminish thus *protecting the capillaries against excessive flooding* with blood Dyspnea tends to diminish but at the price of an increasing burden on the right ventricle A clinical picture resembling cor pulmonale develops Right sided failure with venous engorgement congestion of the liver and often ascites is *prominent The chest pain resembling angina is* not uncommon If hemoptyses appear they are likely to be due to pulmonary infarcts which occur in a high percentage of patients whose emboli originate from the right auricle or leg veins Physical examination reveals the signs indicative of pulmonary hypertension the second pulmonic sound is markedly accentuated and there is a distinct systolic heave over the body of the heart Since flow through the left chambers is diminished there is a *corresponding lessening of intensity* of the presystolic and diastolic murmurs The opening snap is absent or faint X ray shows a marked enlargement of the pulmonary artery as well as of the left and right auricles and of the right ventricle Right ventricular hypertrophy is seen in the electrocardiogram

When the two effects back pressure from the stenotic valve and secondary pulmonary artery constriction are balanced the resulting clinical picture is likely to be that due to a low cardiac output with pronounced lassitude and fatigability but without pronounced pulmonary or systemic congestion The increase in pulmonary vascular resistance is due in part to organic arteriolar changes but it is mainly due to functional constriction since the increased pulmonary resistance may undergo striking improvement *following operative treatment*

A *relative mitral stenosis* with murmurs at the apex simulating mitral stenosis may be found in aortic insufficiency (Austin Flint murmur) patent ductus arteriosus and in various other disorders in which a large flow into the left side of the heart creates a disproportion between the normal mitral valve and the enlarged left ventricle Presystolic murmurs loudest in the tricuspid area may be heard in patients with atrial septal defects and appear to be due to a similar mechanism affecting the right side of the heart These several conditions may be recognized by signs of the basic disorder together with the absence of the opening snap and

the lack of prolongation of the time elapsing between the onset of excitation and the beginning of the first heart sound This Q S[1] time is usually prolonged in patients with mitral stenosis

Mitral Insufficiency Patients with slight incompetence of the mitral valve usually remain free of symptoms but are particularly susceptible to the development of bacterial endocarditis As the lesion becomes more severe dyspnea becomes increasingly pronounced and failure is apt to progress rather rapidly The first sound at the apex is soft or replaced by the loud blowing systolic murmur No opening snap can be heard The apex beat consists of the strong localized thrust indicative of left ventricular hypertrophy On x ray both the left auricle and ventricle are enlarged and systolic expansion of the left auricle may be observed A huge left auricle signifies the presence of a significant degree of mitral regurgitation The electrocardiogram reveals left ventricular hypertrophy

Combined Mitral Stenosis and Regurgitation The introduction of operative treatment for relief of mitral stenosis and the lack of benefit or even harm that occurs when a significant degree of regurgitation is present make the estimation of the relative importance of each of these functional alterations of great importance In many cases the decision can be reached only at exploration In general the more severe and significant the incompetence the louder the systolic murmur at the apex and the more pronounced are the signs of left ventricular hypertrophy by physical fluoroscopic and electrocardiographic examination In these cases the first sound at the apex lacks the characteristic sharpness and loudness of pure mitral stenosis and the opening snap is likely to be absent However one must keep in mind two important possibilities of deception While the opening snap is practically never present when serious mitral insufficiency is present a third sound—the early diastolic gallop indicative of left ventricular failure—may be heard and differentiation between the two will depend primarily on the presence of other manifestations of left ventricular enlargement on the difference in quality of the sounds and on careful timing of the sounds by phonocardiogram Another source of confusion may be the presence of a loud systolic murmur and faint or absent early diastolic or presystolic murmurs This is particularly likely to occur in the most advanced cases of mitral stenosis with severe pulmonary hypertension As already stated the diminished flow through the lungs and left heart tends to dampen the murmurs of mitral stenosis sometimes to extinction In these cases the apical thrust and other signs of left ventricular hypertrophy are absent whereas the signs of pulmonary hypertension are conspicuous [illegible] he systolic murmur tend to be loudest at the tricuspid or pulmonic area In all cases of doubt cardiac catheterization is of great importance

Tricuspid Stenosis This lesion occurs in 3 to 4 per cent of all cases of mitral stenosis The diagnosis is suspected when intractable but nonprogressive right sided heart failure is present for years with little or no dyspnea or orthopnea and when the physical signs of pulmonary hypertension (precordial systolic lift accentuated second pulmonic second sound and electrocardiographic evidence of right ventricular hypertrophy) are slight Ascites is sometimes a prominent feature as is also some degree of icterus due to persistent congestion and fibrosis of the liver A diastolic or presystolic murmur increa ed by inspiration is heard at the tricuspid area X ray reveals conspicuous dilatation of the right auricle without enlargement of the pulmonary artery and the lung fields are characteristically clear

This clinical picture is sometimes witnessed and represents the result of a malady whose preponderant effect is an obstruction at the tricuspid orifice However tricuspid stenosis occurs almost invariably in conjunction with other valvular lesions notably mitral stenosis and the clinical phenomena of "pure" tricuspid stenosis are necessarily modified by the hemodynamic consequences of these other valvular lesions Thus pulmonary congestion with dyspnea on exertion may be a prominent feature even though tricuspid stenosis is present In practice diagnosis of the latter lesion is difficult and frequently missed The only certain method of establishing the diagnosis is by cardiac catheterization and demonstrating a distinct diastolic pressure gradient between right atrium and ventricle

The clinical picture of tricuspid stenosis may be mimicked by more common disorders Thus the Bernheim syndrome is said to occur when a person with a left sided lesion such as aortic stenosis displays the picture of right sided failure and minimal or no evidence of pulmonary congestion This condition has been ascribed to encroachment of a displaced interventricular septum on the right ventricular cavity with impairment of right ventricular filling and flow to the lungs Catheter studies have demonstrated however that pulmonary vascular resistance in such a case is increased indicating the presence of left as well as right ventricular failure Absence of dyspnea is due not only to the impaired blood flow to and from the right ventricle but also to the increased pulmonary arteriolar resistance protecting the capillaries from engorgement

Tricuspid Insufficiency This lesion may be due to congenital displacement of the tricuspid valve (Ebstein's disease) Organic tricuspid insufficiency may also be present when associated with a tri

cuspid stenosis of rheumatic origin The usual cause for this valvular defect is functional stretching of the tricuspid ring and imperfect closure of the leaflets due to right ventricular failure commonly secondary to left sided failure When tricuspid stenosis can be diagnosed with assurance a coexistent organic insufficiency of the valve may be suspected when there is pronounced systolic pulsation of the neck veins and an expansile systolic pulsation of the liver determined by bimanual palpation

Pulmonic Insufficiency Organic disease of the pulmonary valve is practically never of rheumatic origin However functional pulmonary insufficiency with a Graham Steell murmur is common in patients with mitral stenosis and congenital heart disease that is in any condition characterized by a *marked elevation of pressure in the pulmonary artery* The Graham Steell murmur is nearly always faint (grade 1 to 2) and is usually heard best in the left second and third interspaces Differentiation of this murmur from the faint murmur of aortic insufficiency is difficult or impossible unless the peripheral signs of aortic insufficiency are so pronounced as to make the existence of the latter lesion certain In the presence of aortic incompetence and a condition causing pulmonary hypertension the coexistence of a Graham Steell murmur is impossible to ascertain and is not of much importance

Pulmonic Stenosis Pulmonic stenosis due to rheumatic fever is also a rarity Almost invariably this lesion is of congenital origin except for the unusual instances in which it occurs with malignant carcinoid practically always with liver metastases

Surgical Treatment of Rheumatic Valvular Disease

Mitral Stenosis The ideal patient for operation is aged thirty to forty five with progressive exertional dyspnea *which is beginning to interfere seriously* with normal activity with a well marked diastolic rumble and no other murmurs and with clinical electrocardiographic or radiologic evidence of right ventricular hypertrophy but little or no increase in the transverse diameter of the heart If in addition there is a history of hemoptysis of attacks of pulmonary edema or of systemic embolism in such an individual operation is almost imperative *The presence of right sided heart failure* likewise should be considered a reason for carrying out the procedure rather than for postponing it

The absolute contraindications are (1) bacterial endocarditis (2) obvious and outspoken rheumatic activity (3) pronounced mitral insufficiency and (4) clear evidence of mechanically important aortic insufficiency or aortic stenosis unless the aortic valve is to be attacked also

A large percentage of the patients will neither fall into the ideal group nor present the absolute contraindications and then sound clinical judgment comes into play This must be based not only on the clinical evaluation and at times on catheterization data but also on a consideration of the patient s disabilities in relation to his age occupation economic circumstances family responsibility and emotional reactions

It is first necessary to be certain that the patient has mitral stenosis and that the symptoms are due to this lesion and not to some coexistent disorder such as an anxiety state Definitive evidence—clinical radiologic or electrocardiographic—of right ventricular hypertrophy should be present Occasionally it will be doubtful as to whether an apparent presystolic rumble is truly a rumble or a presystolic gallop with a split first heart sound and whether the obvious right ventricular hypertrophy is the result of cor pulmonale or of mitral stenosis In such a case left heart catheterization or the measurement of the *pulmonary capillary* pressure (PC) by cardiac catheterization may furnish decisive evidence The left atrial and pulmonary capillary pressures are not elevated in patients with cor pulmonale but are elevated in individuals with symptomatic mitral stenosis Both conditions of course cause elevation of pressures in the pulmonary artery right ventricle and right auricle

Patients with auricular septal defects and other disorders which increase markedly the blood flow through the tricuspid or mitral orifice may have diastolic rumbles without mitral stenosis In such patients the evaluation of the hemodynamic state may require catheterization of both sides of the heart The presence of a marked conduction defect in the electrocardiogram of a patient with a diastolic rumble should raise the question of an auricular septal defect

A faint apical systolic murmur is not necessarily a contraindication nor is a grade I to III systolic murmur heard loudest in the pulmonic area and unassociated with evidence of aortic stenosis A loud apical systolic murmur (grade III or more) makes it probable that there is a well marked mitral insufficiency even though there is no absolute agreement between the loudness of the murmur and the size of the jet as determined at operation *In a few patients* excellent results have been obtained despite the preoperative presence of signs of outspoken insufficiency as well as stenosis However they are exceptional and in most patients with such findings the postoperative improvement has been slight It is possible that improved operative techniques for reducing the degree of regurgitation will lead to better future results in patients with mitral insufficiency In the meantime catheteri

zation of the left atrium and ventricle with the demonstration of a pronounced diastolic pressure gradient between the two chambers should be a preliminary to operation in a patient of this type The contours of the left atrial pressure curve may yield significant information concerning the relative degrees of stenosis and insufficiency One should be cautious about operation upon a patient with a grade III apical systolic murmur and a short diastolic rumble particularly when there is evidence of left ventricular hypertrophy and an undoubted opening snap is absent In such a patient the rumble may be due to rapid diastolic flow through the mitral orifice with little or no stenosis

Functional pulmonary insufficiency with a Graham Steell murmur is common in patients with mitral stenosis and must be differentiated from aortic insufficiency (Table 110 p 1239) The operation should not be done in a patient who has a basal diastolic blow and who also presents the peripheral signs of aortic insufficiency However when the pulse pressure is less than 40 ml Hg and evidence of left ventricular hypertrophy is absent the presence of a faint diastolic blow is not a contraindication to mitral valvulotomy

When there is unmistakable evidence of well marked left ventricular hypertrophy the likelihood of a good result from the operative procedure is sharply reduced because the chances are strong that the patient has an aortic lesion severe rheumatic myocarditis or outspoken mitral insufficiency

Slight to moderate enlargement of the left atrium speaks for mitral stenosis but a giant left atrium is evidence for pronounced mitral insufficiency and makes it unlikely that a strikingly beneficial effect will be achieved unless the regurgitation can be repaired also

Auricular fibrillation is not a contraindication but if other things are equal the results are likely to be better in patients with regular rhythm

Minimal clinical evidence of smoldering rheumatic activity as indicated by a rapid sedimentation rate or very slight fever is not a contraindication provided one is certain that the mitral stenosis is of long standing and is not the result of edema of the valves Catheterization of the right side of the heart with measurements of the effects of exercise and of digitalis on the pulmonary artery pressure may yield important information as to whether the heart failure is the result of a mechanical valvular lesion or of the myocardial disease

Whether or not auricular fibrillation is present a history of embolism is an indication for operation if preceded by several weeks of anticoagulant therapy

Advanced heart failure is not a contraindication provided one is satisfied that mitral stenosis is the sole cause or even the chief cause of heart failure

A history of acute pericarditis in the past is not a contraindication but adhesions may add to the operative difficulty

Knowledge from long term observation that the signs of mitral stenosis are of recent origin is a contraindication because there is the possibility that the rumble is the result of edema of the valves and that the apparent lesion may disappear with time and with treatment of the rheumatic process

The operation may be done at any age but probably the most desirable range is thirty to forty five years i e after the age of the greatest likelihood of acute flares of rheumatic activity has passed and before senescence of the myocardium has begun

Pregnancy is not an absolute contraindication to the operation but in general the procedure should be postponed until after delivery

Opinions differ as to the long range results Although the operative treatment has now been applied to thousands of patients with mitral stenosis there is still no general agreement concerning the value of the procedure or the criteria for selection of patients Some excellent and critical observers still report a high mortality believe that significant improvement occurs in only a minority of the patients and deem cardiac catheterization essential for proper selection However others report a relatively low mortality (less than 3 per cent) find that the results are good to excellent in the majority of patients submitted to the procedure and consider catheterization necessary in only an occasional instance It is the opinion of the writers that right heart catheterization is indicated when there is doubt concerning the relative importance of myocardial and mechanical factors as well as when the clinical findings suggest tricuspid stenosis Left heart catheterization may help in determining the relative degrees of stenosis and insufficiency of the mitral valve

In the experience of the writers the operative mortality should not be more than 2 per cent if the patients are selected and managed properly Clinical improvement has been striking in many of the patients and sufficient to justify the procedure in most of the others Failure to improve has usually occurred only in individuals who have presented one or more of the contraindications already discussed

The Postcommissurotomy Syndrome This syndrome consisting of pain in the precordium or in the neck is common It may develop a few days or several weeks after the operation and may last for several days only or for a number of months Some investigators have attributed this to reactivation of the rheumatic process others to irritation

cuspid stenosis of rheumatic origin The usual cause for this valvular defect is functional stretching of the tricuspid ring and imperfect closure of the leaflets due to right ventricular failure commonly secondary to left sided failure When tricuspid stenosis can be diagnosed with assurance a coexistent organic insufficiency of the valve may be suspected when there is pronounced systolic pulsation of the neck veins and an expansile systolic pulsation of the liver determined by bimanual palpation

Pulmonic Insufficiency Organic disease of the pulmonary valve is practically never of rheumatic origin However functional pulmonary insufficiency with a Graham Steell murmur is common in patients with mitral stenosis and congenital heart disease that is in any condition characterized by a marked elevation of pressure in the pulmonary artery The Graham Steell murmur is nearly always faint (grade 1 to 2) and is usually heard best in the left second and third interspaces Differentiation of this murmur from the faint murmur of aortic insufficiency is difficult or impossible unless the peripheral signs of aortic insufficiency are so pronounced as to make the existence of the latter lesion certain In the presence of aortic incompetence and a condition causing pulmonary hypertension the coexistence of a Graham Steell murmur is impossible to ascertain and is not of much importance

Pulmonic Stenosis Pulmonic stenosis due to rheumatic fever is also a rarity Almost invariably this lesion is of congenital origin except for the unusual instances in which it occurs with malignant carcinoid practically always with liver metastases

Surgical Treatment of Rheumatic Valvular Disease

Mitral Stenosis The ideal patient for operation is aged thirty to forty five with progressive exertional dyspnea which is beginning to interfere seriously with normal activity with a well marked diastolic rumble and no other murmurs and with clinical electrocardiographic or radiologic evidence of right ventricular hypertrophy but little or no increase in the transverse diameter of the heart If in addition there is a history of hemoptysis of attacks of pulmonary edema or of systemic embolism in such an individual operation is almost imperative The presence of right sided heart failure likewise should be considered a reason for carrying out the procedure rather than for postponing it

The absolute contraindications are (1) bacterial endocarditis (2) obvious and outspoken rheumatic activity (3) pronounced mitral insufficiency and (4) clear evidence of mechanically important aortic insufficiency or aortic stenosis unless the aortic valve is to be attacked also

A large percentage of the patients will neither fall into the ideal group nor present the absolute contraindications and then sound clinical judgment comes into play This must be based not only on the clinical evaluation and at times on catheterization data but also on a consideration of the patient's disabilities in relation to his age occupation economic circumstances family responsibility and emotional reactions

It is first necessary to be certain that the patient has mitral stenosis and that the symptoms are due to this lesion and not to some coexistent disorder such as an anxiety state Definitive evidence—clinical radiologic or electrocardiographic—of right ventricular hypertrophy should be present Occasionally it will be doubtful as to whether an apparent presystolic rumble is truly a rumble or a presystolic gallop with a split first heart sound and whether the obvious right ventricular hypertrophy is the result of cor pulmonale or of mitral stenosis In such a case left heart catheterization or the measurement of the *pulmonary capillary* pressure (PC) by cardiac catheterization may furnish decisive evidence The left atrial and pulmonary capillary pressures are not elevated in patients with cor pulmonale but are elevated in individuals with symptomatic mitral stenosis Both conditions of course cause elevation of pressures in the pulmonary artery right ventricle and right auricle

Patients with auricular septal defects and other disorders which increase markedly the blood flow through the tricuspid or mitral orifice may have diastolic rumbles without mitral stenosis In such patients the evaluation of the hemodynamic state may require catheterization of both sides of the heart The presence of a marked conduction defect in the electrocardiogram of a patient with a diastolic rumble should raise the question of an auricular septal defect

A faint apical systolic murmur is not necessarily a contraindication nor is a grade I to III systolic murmur heard loudest in the pulmonic area and unassociated with evidence of aortic stenosis A loud apical systolic murmur (grade III or more) makes it probable that there is a well marked mitral insufficiency even though there is no absolute agreement between the loudness of the murmur and the size of the jet as determined at operation In a few patients excellent results have been obtained despite the preoperative presence of signs of outspoken insufficiency as well as stenosis However they are exceptional and in most patients with such findings the postoperative improvement has been slight It is possible that improved operative techniques for reducing the degree of regurgitation will lead to better future results in patients with mitral insufficiency In the meantime catheteri

zation of the left atrium and ventricle with the demonstration of a pronounced diastolic pressure gradient between the two chambers should be a preliminary to operation in a patient of this type The contours of the left atrial pressure curve may yield significant information concerning the relative degrees of stenosis and insufficiency One should be cautious about operation upon a patient with a grade III apical systolic murmur and a short diastolic rumble particularly when there is evidence of left ventricular hypertrophy and an undoubted opening snap is absent In such a patient the rumble may be due to rapid diastolic flow through the mitral orifice with little or no stenosis

Functional pulmonary insufficiency with a Graham Steell murmur is common in patients with mitral stenosis and must be differentiated from aortic insufficiency (Table 110 p 1239) The operation should not be done in a patient who has a basal diastolic blow and who also presents the peripheral signs of aortic insufficiency However when the pulse pressure is less than 40 ml Hg and evidence of left ventricular hypertrophy is absent the presence of a faint diastolic blow is not a contraindication to mitral valvulotomy

When there is unmistakable evidence of well marked left ventricular hypertrophy the likelihood of a good result from the operative procedure is sharply reduced because the chances are strong that the patient has an aortic lesion severe rheumatic myocarditis or outspoken mitral insufficiency

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of the pericardium resulting from seepage of blood Cortisone and allied drugs are usually of benefit

Other Valvular Deformities *Tricuspid lesions* constitute an especial problem They are nearly always associated with mitral lesions and the co existent tricuspid disease is not a contraindication to the operation for mitral stenosis The problem is to decide whether to operate on both valves or on the mitral valve alone In most cases this can be decided preoperatively

When a patient who presents clear evidence of mitral stenosis and who is a candidate for opera tive management exhibits signs suggesting tricus pid disease cardiac catheterization should be done in order to measure the diastolic pressure gradient between the right atrium and the right ventricle A gradient of 5 mm Hg or more at the end of diastole is strong evidence for tricuspid stenosis *and makes it desirable that this valve as well as the* mitral valve be dilated at the forthcoming opera tion Tricuspid insufficiency whether organic" or relative is not a contraindication to mitral valvu lotomy

The operative treatment of *aortic insufficiency* and *mitral insufficiency* is still in the experimental stage *Aortic stenosis* is being operated upon suc cessfully by a few surgeons but the technical prob *lems are not yet solved and the mortality remains* high The procedure may result in the production or aggravation of aortic insufficiency even though the stenosis may be improved Once heart failure begins in a patient with aortic stenosis the outlook is extremely poor with conservative management Therefore the attempt at operative correction is justifiable despite the hazard

CORONARY DISEASE

A sharp distinction must be drawn between anatomic and functional disorders of the coronary arteries Seventy per cent of persons beyond the age of fifty have advanced changes in one or more of the larger coronary arteries Atheroma with out significant narrowing probably predisposes to thrombosis and infarction but cannot be diagnosed clinically Marked narrowing even to the point of complete occlusion may exist and cause no clinical manifestations whatever if the collateral circulation is completely adequate There are other instances in which outspoken coronary narrowing without sig nificant myocardial scarring is found at autopsy in elderly patients who during life had congestive fail ure but never presented evidence of angina or of infarction The relative significance of the coronary disease and of the more subtle functional changes due to aging in the production of the congestive failure is uncertain at present Similarly there is uncertainty as to which of the factors is responsible for the outspoken ballistocardiographic abnormali ties so frequently found in such patients The fol lowing discussion is not concerned with asympto matic and clinically unimportant coronary disease nor with those instances of congestive failure in which coronary disease is present but of uncertain clinical significance The concern is rather with those clinical patterns which are specifically and characteristically related to coronary disease

The distinguishing clinical features of sclerosis of the coronary arteries are evidence of past or present myocardial infarction or a history of pain of the anginal type Occasionally a patient may suffer a painless infarction of the myocardium initi ating cardiac symptoms whose origin is clarified by serial electrocardiograms that leave little doubt that coronary disease is present or an electrocardiogram may reveal such characteristic changes in the QRS *complexes as could have resulted from an infarc* tion for which the patient can give no equivalent history Barring these exceptions the diagnosis of coronary sclerosis cannot be made with confidence in the absence of a history of anginal pain or of myocardial infarction and it is only when the manifestations just described are present that the term *arteriosclerotic heart disease* can properly be applied The common use of this diagnosis in elderly *persons with* cardiac *enlargement and congestive* failure in the absence of hypertensive or valvular disease or anginal pain does not at present rest on convincing evidence *The finding of thickening of the radial and brachial arteries does not justify the conclusion that sclerosis of the coronary arteries is present* Actually there is no parallelism between the two processes

Etiology Coronary arteriosclerosis is far more *common in men than in women* The cause of this sex discrepancy has been obscure although there is now evidence that hormonal influences as well as a usually greater internal thickness of the coronary arteries in males may account at least in part for the difference in susceptibility

Aside from the experimental observations that suggest the concept that atherosclerosis represents a disorder of cholesterol metabolism an impressive body of clinical evidence points in the same direc tion This evidence is considered in Chap 228

Clinical Picture The clinical pictures induced by coronary arteriosclerosis are variable In a large percentage of instances no manifestations of illness occur despite extensive disease of these vessels In other individuals relatively slight disease may be associated with severe anginal attacks and sudden death It is apparent that the degree of arterio sclerosis is less important than its rate of develop ment *especially in relation to* the rate of develop ment of collateral circulation through other chan nels When coronary sclerosis does induce clinical

more commonly men past their fiftieth year that they are seized while walking especially if uphill and soon after eating with a painful strangling sensation behind the breastbone that the moment they stand still the pain begins to subside He also pointed out that the pain often extends into the left arm and may appear only here less commonly it appears in the right arm Finally he was familiar with the remarkable termination of the disorder For if no accident intervenes but the disease go on to its height the patients all suddenly fall down and perish immediately

The deviations from this pattern are rather infrequent but they are frequent enough so that some of the more important ones deserve mention Rarely the patient will insist that the pain is burning not constrictive It is not uncommon for the anginal pain to be attributed to indigestion because it occurs after eating but in the majority of such cases the pain is actually precipitated by exercise which happens to be taken immediately after a meal In a small group of patients the pain occurs after a meal even though the patient remains completely at rest Indeed in some of these individuals angina of effort may be absent This unusual behavior is open to two interpretations It may be that some persons are particularly susceptible to the reflex coronary constriction known to occur with distention of abdominal viscera On the other hand it is possible that in such patients increased cardiac output during digestion is not attended by a decline in peripheral resistance such as occurs during exercise Thus the load on the heart after eating may be greater than during walking

Some patients experience their initial attacks only on assuming the recumbent position especially on retiring only later does the angina of effort appear In other patients typical angina appears *not during* the exertion but *immediately after* if they happen to remain quiet in the upright position In these individuals postural hypotension is present and the fall in mean aortic pressure may be sufficient to reduce coronary flow to the point where myocardial hypoxia and anginal pain at rest appear This is particularly likely to happen in persons receiving ganglionic blocking drugs for the treatment of hypertension

Finally the location of the anginal pain may differ from the usual site and offer some difficulty of interpretation Radiation int[illegible] and to the angles of the lower jaw is n[illegible] and the pain may be felt only h[illegible] the pain may be experienced only [illegible] neck at about the level of the l[illegible] or in the left supras[illegible] he left shoulder

The differential [illegible] well as the [illegible]

cussed in a preceding chapter (Chap 4 pp 28 to 33) and need not be discussed here However it should be emphasized again that the response of the pain to exercise and to nitroglycerin as determined by the history and especially by direct observation is usually of much more value than the widely used rule of thumb electrocardiographic studies during hypoxia or exercise Indeed the latter may be misleading

Prognosis Prognosis is more uncertain in this disorder than in any other chronic disease Attacks may cease either following myocardial infarction with destruction of the area responsible for the pain or spontaneously as the result of the development of collateral circulation Apparent recovery may also occur when the individual learns to avoid the precipitating factors In some patients the disorder persists in an essentially static stage for many years the exercise tolerance remaining almost unchanged Increase in severity and frequency of the attacks may follow myocardial infarction and in such individuals it is presumed that the coronary branches are diffusely affected and that the increase in work of the remaining myocardium following destruction of one portion by disease causes the aggravation The important point is that even in patients with an apparently mild form of the disease i e mild in the sense that the pain is minimal and the attacks infrequent sudden death may occur at any time In general however the prognosis is worse when the pain sets in frequently or is of great severity and long duration and is particularly bad when the attacks occur at rest independently of any known precipitating factor

Treatment The management of angina pectoris is frequently effective in ameliorating *symptoms* but rarely completely successful since extensive and irreversible changes are already present throughout the entire coronary tree by the time angina is first manifested The aim is to prevent or halt the progression of further coronary obstruction and to permit the growth of adequate collaterals to the involved areas of myocardial hypoxia Occasionally one does encounter a patient whose angina disappears completely and who lives out a normal life span dying of some unrelated disorder

The tolerance of effort varies so widely that precise directions regarding the amount of permissible exercise cannot be given However the physician can perform a useful service if he emphasizes the principle that any exercise or activity causing pain should be avoided while those not causing pain may be undertaken Exercise below the threshold of pain has never been shown to be harmful and it is possible or even probable that exercise in moderation and always kept below the degree of effort *which induces attacks may have a beneficial effect* Many patients seem to improve when they begin

manifestations either angina pectoris or myocardial infarction may occur As the result of repeated infarction with loss of functioning heart muscle dilatation and congestive failure may supervene However the cardinal clinical pictures associated with coronary arteriosclerosis are those of angina pectoris and of myocardial infarction and these conditions will therefore be discussed in some detail

Angina Pectoris

This disorder may be defined as a clinical syndrome brought about by a temporary discrepancy between oxygen supply and oxygen need in the heart and characterized by a particular type of pain as well as by the likelihood of sudden death Angina pectoris is not a disease in the sense of an etiologic or morphologic entity but like diabetes represents a clinical and physiologic entity The disorder was first clearly delineated by William Heberden whose classic description is a model of astute observation and clear expression

The restriction of the term *angina pectoris* to indicate the pain alone rather than the total syndrome of which the pain is one important feature is justified on neither historical nor clinical grounds

Etiologic Factors Age and sex are important the disease is most common in males beyond the fiftieth year but is observed sometimes as early as the second or third decade In the absence of hypertension or diabetes angina pectoris is rare in women below the age of sixty The other predisposing factors are those which have been mentioned as tending to produce coronary arteriosclerosis—viz obesity diabetes myxedema xanthomatosis and other hypercholesteremic states and the disorders which tend to affect the aortic valve including rheumatic fever and syphilis

The question of the relation of hypertension to angina pectoris is of some importance There is ample evidence that hypertension favors the development of coronary arteriosclerosis The increased work of the heart tends to increase the oxygen needs of the myocardium The increased intramural pressure during systole tends to diminish the systolic coronary flow to the subendocardial portions of the left ventricle On the other hand the higher head of pressure in the aorta tends to increase the systolic flow to the outer portions of the left ventricle and the flow during diastole to the whole heart tends to be elevated as the result of the rise in diastolic blood pressure The over all results of these opposing factors is that angina pectoris is considerably more likely to occur in hypertensive persons than in individuals with normal blood pressure

Aside from the uncommon instances of periarteritis in which coronary involvement causes angina there are scattered reports in the literature of typical cases of angina pectoris occurring in individuals who at autopsy have revealed no gross obstruction of the coronaries and only myocardial involvement by sarcoid scleroderma hemosiderosis amyloid fatty infiltration and endocardial fibroelastosis Presumably in each instance a tiny coronary branch has been narrowed These cases are of interest only as medical curiosities and of importance only at a clinical pathologic conference

The *precipitating causes* (i e the conditions which tend to induce an attack in persons with one of the underlying disorders mentioned) include exercise emotion eating and cold as the most common agents When attacks occur at rest in the absence of these factors they are much more likely to appear in the recumbent than in the sitting or standing postures Such attacks during recumbency are especially likely to occur during sleep Hypoglycemia either induced by insulin or of the spontaneous type is a less frequent precipitating factor but is of considerable practical importance The various types of ectopic tachycardia may induce attacks in predisposed patients and rarely may cause anginal seizures in individuals without disease of the coronary arteries and with structurally normal hearts Since the duration of systole is relatively constant and varies only slightly with variations in heart rate the total amount of systole per minute is increased and the total duration of diastole per minute correspondingly decreased during tachycardia The coronary flow to the fibers of the inner part of the left ventricle tends to be shut off during systole This factor when added to the factor of increased energy expenditure by the heart probably accounts for the occasional occurrence of anginal attacks during seizures of paroxysmal tachycardia in individuals with structurally normal hearts

Of especial importance because of their frequency are attacks of angina occurring during sleep In a few such instances a history indicating nightmares ectopic rhythms or hypoglycemia as the precipitating cause of such attacks can be obtained More common are those patients in which nocturnal reabsorption of fluid from the legs is responsible In such patients the attacks of pain are often associated with dyspnea and both symptoms may be prevented or diminished by restriction of sodium intake and the use of mercurial diuretics However there are other patients in whom no precipitating factor can be found for repeated attacks which awaken the patient from sleep The cause of such anginal attacks is obscure The work of the heart in many elderly persons is greater when the patient is recumbent than when he is sitting

Clinical Picture The majority of patients with angina pectoris give histories that conform closely to the classic pattern originally described so vividly and precisely by William Heberden in 1768 He pointed out that the subjects of the malady are

to take a short walk at a slow pace twice daily after taking a nitroglycerin tablet The distance of the walk should be increased gradually as the exercise tolerance rises Whether the benefits sometimes observed from such a regime are to be attributed to the development of increased collateral circulation in the coronary system or are of psychic origin i e restoration of confidence in a previously frightened patient remains uncertain The patient should be warned that attacks are more easily precipitated if he exerts himself shortly after eating or on a cold windy day and that appropriate reduction in his activity under these circumstances should be made The harmful effects of emotional strain should be particularly emphasized and when necessary a mild sedative or tranquilizer administered

The role of anemia thyrotoxicosis hypoglycemia obesity and paroxysmal tachycardia as possible contributing factors should be kept in mind for these conditions though rather uncommon in patients with angina pectoris are usually readily amenable to treatment

The problem of diet remains highly controversial The importance of cholesterol intake of the amount and kind of fat consumed and of other factors is not yet established For the present the authors believe that the preponderance of evidence suggests the advisability of restricting all fats although recent work indicating the beneficial effect of unsaturated fatty acids (natural vegetable and marine oils) may necessitate a revision of the low fat concept at least for some individuals

The value of beta sitosterol (Cytellin) is sufficiently suggestive to warrant its trial for those who can afford it One to four tablespoonfuls taken with each meal may be required It is probable that beta sitosterol acts by blocking the absorption of cholesterol from the intestinal tract There is no valid evidence for believing that the administration of choline and methionine is of benefit

Large doses of nicotinic acid (1 500 mg after each meal) have been reported to have a favorable effect in lowering the blood cholesterol in patients who can tolerate the flushing and headache which this treatment may produce These untoward effects may be minimized by starting with much smaller doses and gradually increasing them

There is increasing evidence both statistical and experimental that administration of heparin may have a beneficial effect in retarding the development of atherosclerosis and on the clinical course of coronary disease Heparin exerts a complex effect and the factors responsible for the favorable effect on atherogenesis are not known It is believed that the chief factors are the reduction of beta lipoproteins and the removal of fatty coatings from the wall of the intima The anticoagulant effect of heparin in the doses employed is considered to play no role Aqueous heparin is given subcutaneously in doses of 200 mg twice weekly or 150 mg three times weekly Optimal dosage schedules remain to be established

The reversal of the abnormal blood lipoprotein pattern to a more normal one under the influence of estrogens constitutes the basis for the employment of the latter hormones in patients with coronary disease However the feminizing effects with the necessary amounts of estrogens make this method of treatment impracticable for most men Thyroid extract should be administered only with great caution to persons who reveal by accurate tests such as the protein bound iodine an unquestionable hypothyroidism

The treatment of the attack is accomplished most surely by the sublingual administration of nitroglycerin The dose should be sufficient to relieve the attack and slightly less than that which induces flushing of the face and headache 0 15 mg (gr 1/400) to 0 6 mg (gr 1/100) Compared to nitroglycerin other drugs are of relatively little value although occasionally one of the longer acting coronary dilators such as pentaerythrol tetranitrate (Peritrate) 10 to 20 mg t i d may be employed with benefit Rarely a patient with angina and mild postural hypotension may develop syncopal attacks on taking nitroglycerin and such persons should be instructed to lie down immediately after taking the tablet Many patients are reluctant to take nitroglycerin because of the name of the drug or because they will get used to it" so that it may no longer be effective "when they really need it These persons should be assured that it may be safely employed if properly taken not more than 1 tablet every 15 min and that habituation rarely occurs and that the effect is not lost with time although tolerance may be somewhat increased In fact patients should be encouraged to use the drug prophylactically in an attempt to prevent attacks when conditions arise that are likely to lead to seizures

Patients with frequent anginal attacks and especially those with attacks during sleep may be strikingly benefited by the use of nitroglycerin ointment (Nitrol) which the authors have found to be the most effective of the long acting coronary dilators The ointment is spread as thinly as possible (but not rubbed) over the chest abdomen or thighs It is applied every 2 to 4 hr the maximal amount being that which is just short of producing headache —in most patients ½ to 2½ in ointment per dose The beneficial effect lasts 2 to 4 hr The exact dosage and frequency of application of the ointment varies from patient to patient In properly selected cases the improvement resulting from its use may be so striking as to outweigh the dis

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Large doses of nicotinic acid (1 500 mg after each meal) have been reported to have a favorable effect in lowering the blood cholesterol in patients who can tolerate the flushing and headache which this treatment may produce These untoward effects may be minimized by starting with much smaller doses and gradually increasing them

There is increasing evidence both statistical and experimental that administration of heparin may have a beneficial effect in retarding the development of atherosclerosis and on the clinical course of coronary disease Heparin exerts a complex effect and the factors responsible for the favorable effect on atherogenesis are not known It is believed that the chief factors are the reduction of beta lipoproteins and the removal of fatty coatings from the wall of the intima The anticoagulant effect of heparin in the doses employed is considered to play no role Aqueous heparin is given subcutaneously in doses of 200 mg twice weekly or 150 mg three times weekly Optimal dosage schedules remain to be established

The reversal of the abnormal blood lipoprotein pattern to a more normal one under the influence of estrogens constitutes the basis for the employment of the latter hormones in patients with coronary disease However the feminizing effects with the necessary amounts of estrogens make this method of treatment impracticable for most men Thyroid extract should be administered only with great caution to persons who reveal by accurate tests such as the protein bound iodine an unquestionable hypothyroidism

The treatment of the attack is accomplished most surely by the sublingual administration of nitroglycerin The dose should be sufficient to relieve the attack and slightly less than that which induces flushing of the face and headache 0 15 mg (gr 1/400) to 0 6 mg (gr 1/100) Compared to nitroglycerin other drugs are of relatively little value although occasionally one of the longer acting coronary dilators such as pentaerythrol tetranitrate (Peritrate) 10 to 20 mg t i d may be employed with benefit Rarely a patient with angina and mild postural hypotension may develop syncopal attacks on taking nitroglycerin and such persons should be instructed to lie down immediately after taking the tablet Many patients are reluctant to take nitroglycerin because of the name of the drug or because they will "get used to it" so that it may no longer be effective "when they really need it" These persons should be assured that it may be safely employed if properly taken not more than 1 tablet every 15 min and that habituation rarely occurs and that the effect is not lost with time although tolerance may be somewhat increased In fact patients should be encouraged to use the drug prophylactically in an attempt to prevent attacks when conditions arise that are likely to lead to seizures

Patients with frequent anginal attacks and especially those with attacks during sleep may be strikingly benefited by the use of nitroglycerin ointment (Nitrol) which the authors have found to be the most effective of the long acting coronary dilators The ointment is spread as thinly as possible (but not rubbed) over the chest abdomen or thighs It is applied every 2 to 4 hr the maximal amount being that which is just short of producing headache —in most patients ½ to 2½ in ointment per dose The beneficial effect lasts 2 to 4 hr The exact dosage and frequency of application of the ointment varies from patient to patient In properly selected cases the improvement resulting from its use may be so striking as to outweigh the dis

to take a short walk at a slow pace twice daily after taking a nitroglycerin tablet The distance of the walk should be increased gradually as the exercise tolerance rises Whether the benefits sometimes observed from such a regime are to be attributed to the development of increased collateral circulation in the coronary system or are of psychic origin i.e. restoration of confidence in a previously frightened patient remains uncertain The patient should be warned that attacks are more easily precipitated if he exerts himself shortly after eating or on a cold windy day and that appropriate reduction in his activity under these circumstances should be made The harmful effects of emotional strain should be particularly emphasized and when necessary a mild sedative or tranquilizer administered

The role of anemia thyrotoxicosis hypoglycemia, obesity and paroxysmal tachycardia as possible contributing factors should be kept in mind for these conditions though rather uncommon in patients with angina pectoris are usually readily amenable to treatment

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advantages of the cost and its rather unpleasant mode of administration There are certain precau *tions to be observed in its use Postural* hypotension may be induced in elderly patients and tolerance to nitroglycerin may become so increased as to ne cessitate very large doses when sublingual tablets are employed for relief of individual attacks An ginal attacks considerably enhanced in frequency and severity may return if the ointment is suddenly withdrawn Reduction of the dose should be ef fected gradually and over a period of weeks To repeat *the ointment is recommended primarily for the prevention of attacks occurring frequently and particularly when unrelated to exertion*

Patients whose angina is due to aortic stenosis and who do not suffer from myocardial failure have *been relieved of the angina by aortic valve com* missurotomy although the risk of the operation is still considerable

In patients with nocturnal angina sodium re striction and mercurial diuretics are often valuable especially when there is dyspnea associated with the pain

Anginal pain may be relieved by interruption of appropriate nerve pathways but this type of pro cedure is practically never required The various surgical operations aimed at increasing coronary flow are still in the experimental stage

Tobacco should be restricted to a few cigarettes a day or given up completely This advice is espe cially important if smoking can be demonstrated to cause anginal pain premature beats or pro nounced increase in heart rate or blood pressure Alcohol in moderation is permissible and indeed desirable if experience indicates that for the par *ticular individual it exerts a relaxing influence* Cof fee is allowed provided it does not cause palpitation and sleeplessness

Preinfarctional Angina

The choice of a suitable designation for the inter mediate form of coronary pain one that does not fall into the category of effort angina of brief dura tion or the prolonged pain with unquestionable manifestations of myocardial necrosis is difficult Coronary insufficiency and coronary failure are not accurate *since any pain due to hypoxia of the* myocardium whether brief or prolonged is due to insufficiency or failure of the coronary circulation Status anginosus simply implies a prolonged pain but does not indicate whether or not infarction is present Prolonged angina without evidence of myocardial necrosis" appears to be the most ac curate designation but is clumsy The authors sug gest *preinfarctional angina* not because it is free of objections but since prolonged angina is actually a forerunner of infarction in many instances and since from a physiologic standpoint it is but one step away from the stage of myocardial necrosis it appears to them to be the most descriptive of the condition under consideration

Prolonged and usually severe anginal attacks appearing at rest or with minimal exertion are likely to be observed under any of three condi tions In a few patients they may be induced by an *increased load on the heart* such as severe emo tional stress an unusually large meal an episode of hypoglycemia or the excessive ingestion of salt When the cause is removed the patient will usually return to the previous state *having only brief and* milder pain with exertion

Less frequently severe and prolonged angina is initiated by some condition such as dehydration hemorrhage shock ectopic tachycardia or pulmon ary embolism which *reduces cardiac output* and thus causes further decline in blood flow through a coronary system already compromised by atherom atous disease Of particular importance are those instances in which the circulatory failure induced by an initial myocardial infarction leads to ischemic pain in other myocardial regions and thus to the threat of a second and more serious infarction within a few days after the first

More commonly however these prolonged and severe anginal attacks are not associated with demonstrable increase in load or decline in output but apparently with a slow progression of coronary atheroma and an *increasingly unfavorable balance between narrowing of main branches and widening of collateral channels* The patient now begins to have attacks of increasing severity and duration on less and less exertion and to be awakened fre quently by the seizures This is the usual type *of preinfarctional angina Electrocardiographic* changes may be absent or minimal but records obtained during an attack of pain will usually ex hibit depression of S T segments

The distinction between preinfarctional angina and myocardial infarction *depends largely upon* the absence or presence of the signs of tissue necrosis (leukocytosis elevation of serum transami nase fever and an abnormally rapid sedimentation rate) Other features pointing toward infarction include even longer duration of pain *failure of benefit from glyceryl trinitrite the appearance of* a pericardial friction rub development of pulmonary edema and circulatory collapse presence of Q waves and elevation of the S T segment in appropriate electrocardiographic leads The distinction between the two conditions is somewhat artificial because careful study indicates that many of the patients with typical preinfarctional angina display clear evidence of necrosis (transient leukocytosis mini *mal fever elevation of the sedimentation rate) even* though the other manifestations of infarction are absent In such instances one is presumably deal

ing with a small area of necrosis surrounded by a large zone of ischemia The work of Prinzmetal and his associates has demonstrated that the absence of characteristic electrocardiographic changes indicative of infarction means only that the subepicardial region of the heart has been undamaged Since it is the endocardial surface of the myocardium that is more likely to be involved in a small infarct it is not surprising that confirmatory electrocardiographic proof of the infarction is usually wanting The authors think it probable that when these attacks occur out of the blue a partial or even complete closure of a coronary branch has taken place and that the collateral blood supply to the involved area maintains a tenuous balance between supply and need

Preinfarctional angina is the most dangerous type of coronary disease because the patient faces not only the hazard of repeated severe anginal attacks but in most instances the additional hazard of a forthcoming myocardial infarction Thus measures to minimize the size of such an infarct are urgently indicated and frequently appear to be successful The patient s activity should be restricted to the quiet of a hospital room Heparin should be administered for several weeks or longer in dosage adequate to produce the desired anticoagulant effect and also because of its action on the lipoproteins A low fat low caloric diet with frequent small feedings should be instituted Nitroglycerin ointment should be spread thinly on the skin every 3 to 4 hr in dosage sufficient to prevent anginal attacks and sublingual tablets used to treat the pain if it should occur

Myocardial Infarction

Although partial descriptions of the clinical picture of this disorder had appeared in the literature from time to time for many years it was not until the clear discussions of James B Herrick in 1912 and 1919 that the condition began to be recognized generally

The terms *coronary occlusion coronary thrombosis* and *myocardial infarction* are often used synonymously Actually coronary occlusion may be the result of embolism or more commonly may be the consequence of gradual arteriosclerotic narrowing without actual thrombosis Coronary occlusion with or without thrombosis may lead to infarction when the occlusion develops rapidly and may be associated with no infarction when the process is slow Gradual progressive narrowing of coronary vessels resulting in partial occlusion may be associated with anginal attacks of progressively increasing severity and duration (p 1264) and such attacks may persist over a period of several weeks without the development of myocardial infarction if an adequate collateral circulation develops and terminates the attacks Under certain circumstances such as prolonged paroxysmal tachycardia myocardial infarction may develop without actual structural occlusion of the coronary vessels Such considerations make it clear that the interrelationship between coronary occlusion coronary thrombosis and myocardial infarction is not simple Actually coronary thrombosis and coronary occlusion are often recognizable only by post mortem examination On the other hand myocardial infarction produces a characteristic clinical picture which will usually lead readily to the correct diagnosis

Etiology The etiologic factors concerned are essentially those already discussed in regard to coronary arteriosclerosis and angina pectoris The fundamental pathologic process in the great majority of instances is an atheromatous change and myocardial infarction may result from gradual narrowing of the lumen due to such atheromatosis or from the development of a blood clot at the site of the atheroma A less common cause of acute myocardial infarction is a subendothelial hemorrhage in the wall of a coronary vessel Among the rarer causes of myocardial infarction are periarteritis and occlusion of a coronary o tium by luetic aortitis or dissecting aneurysm

Clinical Picture The patient is seized with a *chest pain similar to that of angina* except that *it is unrelated to exertion* It is more intense and prolonged tends to radiate more widely and is not influenced by nitroglycerin The pain usually is described as having a constrictive quality it tends to reach a peak rapidly and it remains at this level without wavering from moment to moment in other words *it is a steady pain not affected by bodily movements or breathing or swallowing—an extremely important diagnostic feature* Shortly after the onset of the pain the patient becomes dyspneic weak and faint nausea and vomiting are common At this time the skin is pallid cool and moist and the blood pressure is considerably lower than the previous levels In milder cases the blood pressure during the first half hour of the attack may be higher than prior levels The heart rate is increased to 100 to 120 the sounds are faint a gallop rhythm is frequently heard and fine and medium moist rales are audible at the bases of the lungs After a variable period of time the manifestations of shock disappear and the pain gradually subsides leaving behind a dull ache that may persist up to a day or so Within a few hours after the beginning of the pain leukocytosis and increased transaminase levels followed by fever are observed still later usually some time between 24 and 48 hr after the onset the sedimentation rate becomes elevated In severe instances the white blood count rises to 12 000 to 20 000 and remains elevated for about 10 to 14 days the fever reaches levels of 100 to 103 F and

subsides in about 7 to 10 days the sedimentation rate is increased for 3 or 4 weeks In about 80 per cent of the cases alterations in the electrocardiogram characteristic of myocardial infarction are noted from the onset of the attack S T elevations followed by inversion of the T waves and the appearance of Q waves In the remainder of the cases the electrocardiographic abnormalities absent in the first day or two are usually observed within 7 to 10 days when daily tracings are made and in a small minority only minor and nonspecific abnormalities are noted even in the presence of an otherwise classical clinical picture

After the first day or two when the pain has usually disappeared the patient may be so free of subjective symptoms that it may be difficult to persuade him of the seriousness of the attack and *of the necessity of several weeks of careful management* The gallop rhythm and the basilar rales may persist for as long as 2 or 3 weeks Some time during the first week usually after the first day and before the seventh a pericardial friction rub may be heard in about 10 to 15 per cent of the cases The pericarditis is usually asymptomatic

The above description applies to patients suffering an attack of moderate severity In patients with milder attacks there may be few or no manifestations of forward or backward failure and the evidence of myocardial necrosis (leukocytosis fever and elevated sedimentation rate) may be correspondingly inconspicuous Almost invariably however at some time during the first week some slight increase in the white cell count or temperature or sedimentation rate may be noted provided the appropriate observations are made sufficiently frequently

In the most severe cases all the symptoms described in the typical case are intensified Forward failure is profound and the patient remains in a state of shock for a number of hours or even days death being prevented only by the vigorous administration of pressor amines At the same time backward failure in the form of pulmonary edema and later systemic congestive failure are more pronounced

The severity of the attack is judged not by the extent of the electrocardiographic alterations but by the clinical picture and the evidence of myocardial necrosis The more severe the clinical manifestations of shock and congestive failure the higher and longer the duration of fever leukocytosis transaminase and sedimentation rate elevation the greater has been the myocardial damage regardless of the appearance of the electrocardiogram The converse is also true when all the above phenomena are minimal the myocardial insult has been small even in the face of an electrocardiographic appearance of "massive infarction (Q waves and absent R waves across the entire precordium) The electrocardiogram is invaluable in substantiating a clinical impression of acute myocardial infarction it is of little value in informing as to the gravity of the attack

In some patients the infarction may be painless It is impossible to state the percentage of patients in whom a painless infarct develops since in some a routine electrocardiogram may reveal the characteristic pattern of infarction without any corresponding history in the past In these persons the myocardial necrosis and repair have proceeded so silently as to have never caused any discomfort of which even an alert person was aware In others the symptoms were so mild that the patient never considered it necessary to consult a physician In still others the classical picture minus the pain may be witnessed sudden development of symptoms and signs of forward and backward failure with shock pulmonary edema electrocardiographic abnormalities etc When pain is absent or atypical and when electrocardiographic changes are minimal the diagnosis may be obscure Especially confusing are those exceptional instances in which the decline in blood pressure may lead to focal neurologic disturbances such as convulsions or hemiplegia These disturbances may dominate the picture myocardial infarction being overlooked In most of the cases of acute painless infarction however the initial symptom is severe dyspnea sometimes associated with acute pulmonary edema

Complications In enumerating the untoward events responsible for practically all deaths in acute myocardial infarction no attempt will be made to differentiate between those occurrences that are more accurately considered inherent consequences of the primary disorder and those that should be strictly designated as complications When the former reach a certain degree of intensity they introduce special problems of management

Shock When at the onset of the attack the systolic level falls below 80 to 90 mm Hg in a previously normotensive person or below 110 to 120 mm Hg in a previously hypertensive patient and remains at these low levels for 2 hr or more and when this fall is associated with the clinical picture of shock—skin pale and drenched in sweat profound weakness clouding of the sensorium peripheral arterial pulsations impalpable—the prognosis is extremely grave over 90 per cent ending in death The cause of the shock is not fully understood a major factor must be the sudden drop in cardiac output Whether in addition obscure reflexes play a contributing role is not known Even if the patient survives this period of shock serious complications resulting from the prolonged hypotension and peripheral vasoconstriction may ensue acute tubular necrosis of the kidneys focal cerebral disorders

gangrene of the skin and muscle in the extremities and further extension of the infarcted area in the myocardium

Acute Pulmonary Edema In the earliest stages of a severe attack the sudden impairment of contractile power of the left ventricle may lead to serious or fatal pulmonary edema This is usually associated with more or less severe shock signs of systemic congestive failure are absent If the patient survives for more than a day or two and left ventricular contractile power fails to recover or if he has practically recovered and a complication supervenes that imposes an additional burden on the left ventricle (ruptured septum new infarction ectopic tachycardia etc) the picture of systemic congestive failure appears

Abnormal Rhythms The appearance of an ectopic tachycardia which may be of any type may suddenly alter the course from one that is progressing favorably to one of grave danger The harmful effect of these arrhythmias is due to the rapid rate and the resulting abbreviation of diastole Ventricular tachycardia presents an additional danger since it is the forerunner of fatal ventricular fibrillation Heart block of either second or third degree introduces the risk of ventricular standstill or fibrillation

Rupture of the Myocardium Rupture of the free wall of the ventricle at the site of the infarction with rapid development of cardiac tamponade occurs in about 10 per cent of the fatal cases This is apt to develop during the first 14 days and death occurs so rapidly that it is rarely possible to determine which of the causes of sudden death has been responsible Rupture of the interventricular septum is much less common The diagnosis is suggested by the appearance of a loud systolic murmur at the lower left sternal border often associated with a systolic thrill the rapid increase in congestive failure and death within a week Rarely a patient with this complication may live for several years Far more uncommon than either of the above forms of rupture is the rupture of an infarcted papillary muscle which is responsible for the sudden appearance of murmurs loudest at the apex and the development of fatal pulmonary edema within a few hours

Thromboembolism Systemic embolism arising from left ventricular mural thrombi may lead to serious or fatal complications gangrene of legs hemiplegia occlusion of abdominal vessels etc Much more common are pulmonary emboli sometimes due to a right ventricular mural thrombus overlying a septal infarct but far more often due to emboli originating in the deep veins of the legs Finally a second myocardial infarct due to development of another coronary thrombosis may occur while the patient is recovering from the first

Prognosis In this condition as in angina pectoris *prognosis is always uncertain There is perhaps no* other disorder in which a patient apparently pro*gressing favorably is so likely to die unexpectedly* Likewise there are few conditions in which a patient so seemingly moribund may recover to assume eventually a life of relatively normal activity In general the prognosis is better in middle-aged than in elderly patients because the younger individuals are less apt to have advanced sclerotic changes throughout the coronary tree and perhaps especially because the older patients are more apt to have serious concurrent disease such as latent senile heart disease prostatic enlargement emphysema etc The prognosis is likely to be better when the infarction sets in suddenly than when it is preceded by prolonged and severe attacks of angina pectoris (p 1264) The appearance of severe con*gestive failure adds to the gravity of the outlook as does persistence of the pain beyond a period of 1 or 2 days*

Frequent ventricular premature beats sometimes precede the development of ventricular tachycardia and hence should be viewed as an unfavorable sign particularly if they do not disappear on administration of quinidine The gravity of prolonged shock severe pulmonary edema and the various ectopic tachycardias has already been mentioned The outlook when these rapid rhythms supervene depends on the promptness with which they can be terminated The danger with ventricular tachycardia arises from the fact that even after one paroxysm has been stopped another may start and progress to fatal ventricular fibrillation or cause death by myocardial failure despite the use of quinidine in the usual prophylactic doses In general if the patient has surmounted the initial insult to the myocardium with its attendant shock and pulmonary edema and has survived beyond 14 days when myocardial rupture and ectopic rhythms are most likely to occur the chief risk is the development of a thromboembolic complication At no time however is the risk of sudden death due to ventricular standstill or fibrillation absent

Treatment The first principle is that the treatment should be directed at the patient rather than at the electrocardiogram This is especially important in the decisions concerning activity and return to work

During the first few hours complete rest is indicated and sufficient opiates or other analgesics should be used to relieve the pain Food may be restricted to fruit juices for the first 24 to 48 hr and water given in amounts of 1 000 to 1 500 ml or more depending on the extent of the loss by sweating Enough fluids should be given to ensure a urinary output of at least 700 ml The intravenous route for administration of fluids and drugs should be avoided except when imperative

If there are numerous rales in the lungs or if cyanosis is present oxygen is urgently needed Even in the absence of these signs oxygen is probably of value as the elevation of arterial oxygen content although small in degree will allow a given level of tissue oxygen tension to be achieved at a lower level of cardiac output and may therefore rest the heart It has been demonstrated in animals that the oxygen content of the marginal areas around the infarct is increased by the administration of oxygen

Opinions differ concerning the value of the use of coronary dilator drugs during the acute phase There is experimental evidence against the value of theophylline derivatives (aminophylline) which have been shown to increase cardiac work more than coronary flow The clinical evidence for the use of atropine and papaverine is not convincing Theoretically drugs which dilate the coronary arteries without causing significant decline in blood pressure would be expected to be beneficial

There is evidence now disputed that anticoagulant therapy may be of great value in the management of patients with myocardial infarction The purposes of such therapy are to prevent phlebothrombosis and hence reduce the likelihood of pulmonary embolism and infarction to prevent further thrombosis in the coronary vessels and to prevent mural thrombosis

Anticoagulant therapy may increase the gravity of cerebral or other embolisms and there is evidence that hemopericardium with or without rupture of the myocardium is about twice as frequent when Dicumarol is employed It is generally agreed that anticoagulant therapy should be used in the severer forms of myocardial infarction but there is conflicting opinion about the advisability of its use in the milder (good risk) forms Nevertheless it is difficult to ignore the possibility that even in a good risk patient an embolus from a mural thrombus may be catastrophic When Dicumarol or some similar drug affecting the prothrombin content of the blood is employed reliable laboratory control is essential and vitamin K_1 (Mephyton) should always be immediately available if hemorrhage or dangerous prolongation of prothrombin time occurs These drugs are contraindicated when significant disease of the liver or kidney or a recently bleeding ulcerative lesion is present

Heparin is usually employed only during the first 2 to 3 days until the prothrombin time has been increased to therapeutic levels It is ordinarily not used as the sole anticoagulant agent because parenteral injection is required and also because of its expense Nevertheless the authors believe there are sound reasons for using heparin exclusively The administration of aqueous heparin intravenously or with a small amount of procaine subcutaneously with a very small caliber needle is practically painless The expense of the heparin is largely offset by the avoidance of the daily prothrombin time estimation necessitated when Dicumarol is used since a fairly constant elevation of the coagulation time to therapeutic levels can be maintained once the proper dose of heparin has been ascertained The antithrombin effect of heparin is greater and more reliable as an anticoagulant than is the antiprothrombin effect of Dicumarol Should bleeding occur or the coagulation time be raised excessively protamine sulfate has an almost immediate neutralizing effect Finally there is evidence that heparin exerts a beneficial effect in coronary disease aside from its capacity to prolong coagulation time

Aqueous heparin should be given every 8 hr in an amount sufficient to increase the coagulation time to three to four times the pretreatment level The usual dose is 40 to 100 mg Depot heparin should not be employed since absorption is too irregular to give reliable results

After the initial stage has passed and the pain has ceased the problem of therapy changes somewhat The diet should be low in sodium low in calories (800 to 1000 cal) low in cholesterol and generous in ascorbic acid which may perhaps have a favorable effect on the healing of the infarct Pending more complete knowledge it would seem wise to administer ascorbic acid in oral doses of about 300 mg per day for the first 3 weeks

One of the major problems in the management of patients with myocardial infarction involves the decision concerning the duration and rigidity of restriction of activity There should be no fixed rules the program depending on the severity of the illness and to a lesser degree on the temperament of the patient Ordinarily the semirecumbent posture will be preferable when there is slight dyspnea the sitting position when dyspnea is marked and the recumbent position when dyspnea is absent or a shock like state exists Some physicians still advocate rest in bed for a period of several weeks but others including the writers believe that patients should be allowed to sit up in bed as soon as the shock and pain have disappeared and should be allowed to sit in a chair within the next few days It is probable although the evidence is incomplete that there is every advantage in prolonged restriction of activity but no advantage in prolonged rigid rest in bed The question whether the patient should use the bedpan or be allowed to walk to the toilet can usually be answered by adopting the middle course of a bedside commode when the use of the bedpan is attended by discomfort

In order to avoid straining at stool, Colace or Velmol or a mineral oil emulsion should be employed

Mild sedatives of the barbiturate group or reserpine are likely to be useful The latter may be preferable since it may effect a desirable slowing of the heart rate and also a *reduction* of blood pressure in hypertensive patients

During the period of bed rest *it is important that the legs be massaged and that first passive and later active movement be initiated* in order to minimize the likelihood of phlebothrombosis Elastic stockings are also useful in this respect

The discussion thus far has been centered on the management of the milder instances without the more serious complications The latter may now be considered

Treatment of Congestive Failure Congestive failure usually takes the form of pulmonary edema (Chap 226) Intravenous Cedilanid is the procedure of choice The drug is best administered as a slow infusion in glucose solution The usual initial dose for patients not previously receiving digitalis is 1 0 to 2 0 mg administered during a period of 6 to 10 hr while the patient is constantly observed for the appearance of arrhythmias or nausea which was not previously present Once congestive failure is controlled maintenance doses of 0 2 to 0 3 mg Cedilanid can be given twice daily parenterally for a few days After this period one can change to the oral administration of a long acting preparation such as Digitoxin or powdered leaf Because of the rapid excretion of Cedilanid the initial total daily dose of the longer acting preparations will usually need to be about 0 4 mg (*Digitoxin*) or 0 4 Gm (powdered leaf) for 2 to 4 days Then a daily maintenance dose one quarter to one half as great may be administered (p 1311)

The other procedures to be used in the management of congestive failure are discussed in Chap 226

Shock This is a grave complication The signs of forward failure and backward failure (Chap 14) usually coexist Digitalis should be administered as described At the same time vasoconstrictor drugs should be employed as indicated in Chap 271 These too should be administered by slow intravenous drip and should be discontinued if ectopic rhythms including numerous ventricular premature beats develop Norepinephrine is a reliable preparation The dose varies markedly from patient to patient and should usually be administered according to the rate required to maintain a pulse pressure and a systolic pressure of at least 30 and 100 ml Hg respectively (Chap 271) However aside from the level of blood pressure the other signs of shock are important Indeed a well marked lowering of blood pressure even to values as low as 95/65 which is not associated with clammy skin ashen color apathy or lassitude usually requires no treatment

Other procedures such as infusions of blood plasma or salt solution are probably more apt to be harmful than beneficial Some patients with severe forward failure will die despite the use of digitalis and norepinephrine but other seemingly moribund patients will recover

Arrhythmias These frequently occur and should be managed as discussed in the preceding chapter When the disturbances of rhythm occur in a patient with myocardial infarction they are more hazardous and often more difficult to control than under other circumstances Nevertheless they often respond dramatically to treatment which may be lifesaving in such patients

Thromboembolic Episodes These should be prevented by the use of anticoagulants massage of the legs passive and active movements elastic bandages and getting the patient out of bed and into a chair as already indicated When in spite of these precautions pulmonary infarction occurs the question of venous ligation should be entertained (Chap 236)

Rupture of the Heart Transmural rupture is not infrequent during the first 2 weeks but is rare thereafter It may occur during straining at stool Possibly the liberal use of vitamin C tends to prevent it Rupture of a papillary muscle or of the interventricular septum is rare These complications are *not amenable to therapy*

Secondary Skeletal Pain This is common not only in the shoulder arm and hand but also in the pectoral muscles (Chap 4) This type of pain while not of serious physical significance is likely to induce grave anxiety the patient fearing that another heart attack" has occurred Reassurance massage heat and acetylsalicylic acid are valuable When the pain is severe stellate ganglion block or cortisone may produce dramatic relief

Secondary Anxiety States Emphasis has been directed repeatedly at the importance of psychologic management in all cases of disorders of the heart In none are sympathetic understanding and insight into the emotional problems of the patient more necessary than when dealing with individuals who have suffered a myocardial infarct Most of these patients are stricken at the height of their business or professional careers and of their responsibility to family and colleagues The ominous significance of heart attack" and "coronary thrombosis" has attained such wide diffusion among the laity especially through reports of the unexpected deaths of friends who but a few days before had seemed robust and well that hardly anyone who has sustained such an attack can fail to ponder anxiously on what the future will hold for him Aside from the immediate threat to his life the questions of his capacity to carry on his business job or profession and of the far reaching influence this ill

If there are numerous rales in the lungs or if cyanosis is present oxygen is urgently needed Even in the absence of these signs oxygen is probably of value as the elevation of arterial oxygen content although small in degree will allow a given level of tissue oxygen tension to be achieved at a lower level of cardiac output and may therefore rest the heart It has been demonstrated in animals that the oxygen content of the marginal areas around the infarct is increased by the administration of oxygen

Opinions differ concerning the value of the use of coronary dilator drugs during the acute phase There is experimental evidence against the value of theophylline derivatives (aminophylline) which have been shown to increase cardiac work more than coronary flow The clinical evidence for the use of atropine and papaverine is not convincing Theoretically drugs which dilate the coronary arteries without causing significant decline in blood pressure would be expected to be beneficial

There is evidence now disputed that anticoagulant therapy may be of great value in the management of patients with myocardial infarction The purposes of such therapy are to prevent phlebothrombosis and hence reduce the likelihood of pulmonary embolism and infarction to prevent further thrombosis in the coronary vessels and to prevent mural thrombosis

Anticoagulant therapy may increase the gravity of cerebral or other embolisms and there is evidence that hemopericardium with or without rupture of the myocardium is about twice as frequent when Dicumarol is employed It is generally agreed that anticoagulant therapy should be used in the severer forms of myocardial infarction but there is conflicting opinion about the advisability of its use in the milder (good risk) forms Nevertheless it is difficult to ignore the possibility that even in a good risk patient an embolus from a mural thrombus may be catastrophic When Dicumarol or some similar drug affecting the prothrombin content of the blood is employed reliable laboratory control is essential and vitamin K_1 (Mephyton) should always be immediately available if hemorrhage or dangerous prolongation of prothrombin time occurs These drugs are contraindicated when significant disease of the liver or kidney or a recently bleeding ulcerative lesion is present

Heparin is usually employed only during the first 2 to 3 days until the prothrombin time has been increased to therapeutic levels It is ordinarily not used as the sole anticoagulant agent because parenteral injection is required and also because of its expense Nevertheless the authors believe there are sound reasons for using heparin exclusively The administration of aqueous heparin intravenously or with a small amount of procaine subcutaneously with a very small caliber needle is practically painless The expense of the heparin is largely offset by the avoidance of the daily prothrombin time estimation necessitated when Dicumarol is used since a fairly constant elevation of the coagulation time to therapeutic levels can be maintained once the proper dose of heparin has been ascertained The antithrombin effect of heparin is greater and more reliable as an anticoagulant than is the antiprothrombin effect of Dicumarol Should bleeding occur or the coagulation time be raised excessively protamine sulfate has an almost immediate neutralizing effect Finally there is evidence that heparin exerts a beneficial effect in coronary disease aside from its capacity to prolong coagulation time

Aqueous heparin should be given every 8 hr in an amount sufficient to increase the coagulation time to three to four times the pretreatment level *The usual dose is 40 to 100* mg Depot heparin should not be employed since absorption is too irregular to give reliable results

After the initial stage has passed and the pain has ceased the problem of therapy changes somewhat *The diet should* be low in sodium low in calories (800 to 1000 cal) low in cholesterol and generous in ascorbic acid which may perhaps have a favorable effect on the healing of the infarct Pending more complete knowledge it would seem wise to administer ascorbic acid in oral doses of about 300 mg per day for the first 3 weeks

One of the major problems in the management of patients with myocardial infarction involves the decision concerning the duration and rigidity of restriction of activity There should be no fixed rules the program depending on the severity of the illness and to a lesser degree on the temperament of the patient Ordinarily the semirecumbent posture will be preferable when there is slight dyspnea the sitting position when dyspnea is marked and the recumbent position when dyspnea is absent or a shock like state exists Some physicians still advocate rest in bed for a period of several weeks but others including the writers believe that patients should be allowed to sit up in bed as soon as the shock and pain have disappeared and should be allowed to sit in a chair within the next few days It is probable although the evidence is incomplete that there is every advantage in prolonged restriction of activity but no advantage in prolonged rigid rest in bed The question whether the patient should use the bedpan or be allowed to walk to the toilet can usually be answered by adopting the middle course of a bedside commode when the use of the bedpan is attended by discomfort

In order to avoid straining at stool, Colace or Velmol or a mineral oil emulsion should be employed

manly on the left ventricle left sided failure with rise in pressure in the left atrium and consequent pulmonary engorgement may set in suddenly and produce attacks of paroxysmal nocturnal dyspnea or of acute pulmonary edema These attacks may appear as the first manifestation of congestive failure more frequently they occur after appreciable exertional dyspnea has become evident Gallop rhythm and pulsus alternans are observed with especial frequency and when they occur they are ominous signs for they indicate not merely disease but impending or actual myocardial failure Eventually provided the patient does not succumb to an attack of acute pulmonary edema left ventricular failure is followed by failure of the right ventricle and the complete picture of congestive failure is apparent

Treatment The treatment of hypertensive heart disease consists essentially of the treatment of the hypertension plus the management of congestive failure (Chap 226) or of angina pectoris (p 1262) according to which of these conditions exists The increasingly favorable results from the use of antihypertensive drugs (Chap 227) make it likely that cardiac complications may be prevented more effectively in the future than in the past

COR PULMONALE

Although pulmonary hypertension with eventual right ventricular failure may follow any type of left sided heart failure as well as certain congenital lesions the term *cor pulmonale* is applied only to those instances in which the primary cause of pulmonary hypertension is disease of the lungs or of the pulmonary vessels Such a sequence of events may set in acutely following pulmonary embolism of sufficient grade to cause serious interference with the circulation through the lungs The subacute type which endures for a few weeks to a few months may be due to recurrent embolism including that from amniotic fluid extensive miliary carcinomatosis or to any rapidly progressive and widespread infection of the lungs as by miliary tuberculosis or by pyogenic or fungous disease However the usual and the most important type is chronic cor pulmonale

The most common causes of chronic cor pulmonale are emphysema asthma and bronchiectasis which frequently appear in combination with one another Other causes include pneumoconiosis pulmonary fibrosis due to any extensive chronic infection kyphoscoliosis sarcoidosis beryllium granulomatosis and other granulomatoses of undetermined etiology scleroderma schistosomiasis essential pulmonary hypertension Ayerza's disease ("black cardiac") originally ascribed to syphilitic disease of the pulmonary arteries is like the proverbial ghost that is never seen except in a book or by someone else This term if used at all should be applied to the patient with cor pulmonale polycythemia and a severe form of pulmonary insufficiency

Diagnosis Cor pulmonale should be suspected in any individual presenting evidence of any of the above etiologic factors who also reveals signs of right ventricular hypertrophy The dyspnea in these patients is of the pulmonary rather than the cardiac type (Chap 226) and is often relatively slight in the resting state as compared with such prominent manifestations of right ventricular failure as distention of the veins and enlargement of the liver A few of the patients with chronic cor pulmonale have substernal pain almost but not quite identical with the pain of angina pectoris Occasionally syncope on exertion occurs The signs indicative of right ventricular hypertrophy are the systolic lift over the body of the heart the increased second pulmonic sound and the roentgenologic evidence of enlargement of the pulmonary artery and its main branches and of the right ventricle Electocardiographic evidence of right ventricular hypertrophy is a late phenomenon and its absence does not exclude cor pulmonale Cyanosis polycythemia and clubbing of the fingers signify the presence of long acting arterial hypoxemia Clubbing alone may be due to bronchiectasis Hydrothorax is rare in failure due to uncomplicated cor pulmonale The arm to lung (ether) circulation time may be prolonged but the lung to tongue (Decholin minus ether) time is usually normal This is the reverse of the situation when dyspnea is of cardiac origin

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When anatomic restriction of the pulmonary bed is relatively slight but is associated with arterial hypoxemia (saturation less than 85 per cent) that may be caused by a variety of mechanisms—hypoventilation impairment of diffusion venoarterial shunts uneven ventilation in relation to blood flow—the situation becomes more complicated Severe hypoxemia is associated with carbon dioxide re

ness will have on the lives of his wife and children must obtrude on his thoughts It is not necessary to discuss the innumerable anxieties that inevitably attend the convalescence of the person who lies in bed or leads the restricted life following the acute attack Suffice it to say that these ideas do pre occupy a large part of his thoughts and recognition of their existence must not be overlooked by the physician however impassive and philosophic the patient may seem to be It is during these days that the *physician must exert his utmost skill in* restoring confidence in explaining in simple terms the significance of the illness and in allaying fears and anxieties The task is not easy for the physician cannot forget that behind the apprehensions of the patient there is a core of truth that can never be dissipated He can however come to a reasonably accurate estimate as to the degree of activity in which the patient may ultimately participate and he can within the limitations imposed by a malady of such uncertain course encourage a life that will often be more active and useful than the patient had imagined He can point out the many useful and productive years that others suffering from the same disorder have experienced The details and the intricacies of this problem will be as varied as the temperaments and the circumstances sur rounding each individual patient The administra tion of drugs and the supervision of strictly medical measures constitute a progressively diminishing part of the total management as the days of the acute attack recede and the days of convalescence and resumption of more or less normal life progress

The question arises as to how soon a patient should resume his work after a myocardial infarc tion The answer should never be based on the electrocardiogram alone but rather on the total clinical picture the severity of the attack and the rate and completeness of recovery as well as the nature of the patient s occupation There can be no rigid rules Certainly the patient who has sustained a relatively small infarction as judged by the ab sence of shock and myocardial failure and the pres ence of minimal electrocardiographic alterations fever leukocytosis and elevation of sedimentation rate should be managed altogether differently from the person in whom all these data have indicated an extensive area of necrosis Consequently some individuals may logically be permitted to return to work within 4 to 6 weeks after the onset of the attack Others may require many weeks or months or may never be able to work again particularly when the occupation is one in which strenuous physical exertion is unavoidable In all cases the return to work should be gradual and full activity assumed only under careful and frequent observa tion Most patients will benefit by a permanent plan of a noon rest period of 1 hr Activities which in duce tension fatigue dyspnea or anginal pain should be permanently forbidden

Smoking in moderation (8 to 12 cigarettes daily) may be allowed in most instances but should be forbidden to those patients who develop pain un due rise in blood pressure tachycardia or prema ture beats following smoking The possible value of the ballistocardiogram as a guide to the harmful effects of smoking has already been mentioned There is no evidence that alcohol in moderation *i e 1 to 3 oz of whisky per day is harmful and* none that it is beneficial other than through its sedative action

The diet employed for patients with angina pec toris should be followed permanently by patients who have recovered from an acute myocardial in farction

HYPERTENSIVE HEART DISEASE

The discussion to follow will deal not with the question of hypertension in general which will be discussed in Chap 227 but only with heart disease resulting from hypertension

Elevation of blood pressure is the most common cause of congestive heart failure among patients in the forty to fifty five year age group it accounts for a minority of the instances under the age of forty and when coupled with senile change is fre quently an important factor in the production of congestive failure in patients in the seventh and eighth decades About one half the individuals with hypertension will eventually develop congestive failure although this complication usually does not occur for many years

Hypertension is also an important etiologic factor in relation to angina pectoris (p 1261)

Hypertensive heart disease is that form of heart disease that is associated with long continued in creased arteriolar resistance and is presumably due largely if not entirely to the increased work of the left ventricle contracting against a permanently increased peripheral resistance

A sustained increase in the blood pressure usually leads to left ventricular hypertrophy (p 1234) in some cases so slight as to be clinically undetectable and insignificant This is often the sole manifesta tion of early hypertensive heart disease

Clinical Course Following the discovery of the hypertension a number of years may elapse 10 or 20 or even 30 before symptoms referable to the heart develop if they develop at all This may be true even though levels as high as 240 systolic and 120 diastolic have been obtained during a large part of this time In some the clinical picture is that of coronary disease angina pectoris or myo cardial infarction In others a much larger group congestive failure ensues Because the strain is pri

mainly on the left ventricle left sided failure with rise in pressure in the left atrium and consequent pulmonary engorgement may set in suddenly and produce attacks of paroxysmal nocturnal dyspnea or of acute pulmonary edema. These attacks may appear as the first manifestation of congestive failure more frequently they occur after appreciable exertional dyspnea has become evident Gallop rhythm and pulsus alternans are observed with especial frequency and when they occur they are ominous signs for they indicate not merely disease but impending or actual myocardial failure Eventually provided the patient does not succumb to an attack of acute pulmonary edema left ventricular failure is followed by failure of the right ventricle and the complete picture of congestive failure is apparent.

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When anatomic restriction of the pulmonary bed is relatively slight but is associated with arterial hypoxemia (saturation less than 85 per cent) that may be caused by a variety of mechanisms—hypoventilation impairment of diffusion venoarterial shunts uneven ventilation in relation to blood flow—the situation becomes more complicated Severe hypoxemia is associated with carbon dioxide re

tention and respiratory acidosis The hypoxia increases the already existent but mild pulmonary hypertension and this effect is further enhanced by the increased cardiac output secondary to the hypoxia Hypoxia also stimulates the production of red blood cells blood volume and viscosity increase and both aggravate pulmonary hypertension still further Right ventricular dilatation and hypertrophy and eventually failure take place primarily because of the pulmonary hypertension but also because of the increased cardiac output and possibly through a direct effect of hypoxia on the myocardium Cardiac output declines but may still be above the normal level plasma volume increases and one more straw is added to the already numerous burdens overwhelming the pulmonary circulation and right ventricle

Prognosis Prognosis in cor pulmonale depends on how many and how effectively the reversible factors contributing to pulmonary hypertension can be influenced Pure fibrosis with extensive and irreversible vascular lesions and essential pulmonary hypertension represents one extreme of a spectrum whereas uncomplicated chronic obstructive emphysema exemplifying a type of disorder largely dependent on functional and ameliorable derangements represents the other and more favorable end of the spectrum of respiratory disorders leading to cor pulmonale There are all gradations between

Treatment The acute development of failure in cor pulmonale due to emphysema is usually brought on by some new pulmonary disorder that diminishes an already compromised respiratory reserve A reasonably tolerable situation may be quickly converted into one of grave urgency The precipitating factor is usually an acute respiratory infection though it may be a pulmonary infarction or passive congestion of the lungs due to an unrelated cardiac disorder *The immediate obligation is to improve respiratory function and relieve hypoxia* The following general principles are important

1 *Avoidance of drugs that depress the respiratory center* The patient is often very restless and in distress Nevertheless morphine codeine and related drugs should be prohibited even barbiturates should be used with caution or avoided and sedation should be accomplished with chloral hydrate paraldehyde or one of the tranquilizing drugs

2 *Treatment of infection* Vigorous treatment of even mild acute infections should be instituted promptly by the administration of large doses of penicillin or other antibiotics depending on sputum culture and appropriate sensitivity tests

3 *Measures to facilitate ventilation* Steam inhalations and expectorants such as potassium iodide (15 drops of the saturated solution t i d) are valuable Bronchodilator drugs are extremely important

a Epinephrine 1 per cent or phenylephrine 1 per cent (Neo synephrine) or isopropyl norepinephrine 0 5 per cent (Isuprel) should be given as an aerosol either by a hand operated nebulizer or by a nebulizer attached to an oxygen tank the flow of oxygen being set at 6 or 7 liters per minute Five drops of one of these solutions is administered every 4 to 6 hr 1 drop of glycerin being added to minimize the feeling of dryness of the throat and the oxygen is bubbled through a column of water When the secretions are thick and tenacious the bronchodilator drug should be added to 1 0 ml Alevaire

b Aminophylline 0 25 to 0 5 Gm may be administered intravenously two to four times a day or since dehydration is often present by intravenous drip 0 5 Gm in 5 to 10 per cent glucose solution twice daily In many cases aminophylline 0 5 Gm by rectum either in a suppository or dissolved in 120 ml water is effective

c When wheezing is pronounced *cortisone* 100 mg t i d by mouth or corticotropin (ACTH) intramuscularly 40 mg daily in a slow acting form or 20 mg in a 5 to 10 per cent glucose solution drip may be extremely valuable in tiding the patient over the first few stormy days after which the dose should be tapered off to the minimal effective maintenance dose of cortisone Cortisone may also be given for sarcoidosis or other granulomatous lesions and a temporary improvement may be effected

d Mechanical respirators have been employed with great benefit in very ill patients in order to ensure adequate ventilation However the cost of the apparatus and the complexities involved in its use have thus far limited this procedure to a relatively few centers particularly interested in the problem

4 *Oxygen therapy* This should be used cautiously at first and then intermittently since when severe carbon dioxide retention has been present over a long period of time carbon dioxide narcosis may be induced sometimes suddenly when oxygen therapy is employed continuously

5 *Reduction of blood volume and viscosity by venesection* After the first 2 or 3 days this procedure should be instituted if the hematocrit is elevated 300 to 500 ml of blood being removed every 2 to 3 days until the hematocrit level is lowered to 45 to 50 per cent and provided the hemoglobin does not fall below 12 Gm

6 Therapy for congestive failure given alone is ineffectual with the therapeutic procedures described above rest digitalis low sodium diet and mercurial diuretics are of benefit

The various measures described above are employed with striking success when the problem is solely or largely chronic diffuse obstructive emphy

sema One is dealing with an illness of which one of the *most important components is a functional* derangement—hypoxia—that can be combated When recovery from the acute disorder has been obtained further therapy is that of the underlying emphysema For the patient with fibrosis or irremediable vascular disease little can be done beyond the usual procedures for congestive failure and *any* coincidental complications The outlook is dismal

SYPHILITIC HEART DISEASE

With rare exceptions syphilitic disorders of the heart are secondary to *involvement of the aorta* Syphilitic aortitis is discussed in Chap 229 and the discussion here is concerned only with such aspects as affect the heart directly These include the problems of angina pectoris and aortic insufficiency

Diagnosis Syphilitic aortic insufficiency should be suspected when a middle aged individual usually a male lacking a story of rheumatic fever presents the classic manifestations of aortic regurgitation *The suspicion is strengthened* when there is a history of a primary lesion or of antisyphilitic treatment in the past and when the serologic tests *for syphilis are positive (they are positive in about* 85 per cent of such cases) The tambour quality of the second heart sound at the aortic area is *often present but is also heard in patients with* aortic atheroma or hypertension Hence it is significant only when heard in a comparatively young *patient with a normal blood pressure*

Although syphilis does not produce deformity of the mitral valve the dilatation of the mitral ring *consequent to aortic regurgitation frequently causes* an apical systolic murmur Furthermore the Austin Flint murmur ("relative mitral stenosis) is frequently heard *in patients with syphilitic aortic re*gurgitation and this murmur cannot be differentiated with certainty from the similar murmur of mitral stenosis *Rough basal systolic murmurs are* commonly present and rarely a systolic thrill is felt but other evidence of aortic stenosis is not encountered *Hence the decision as to whether* in a given individual presenting aortic insufficiency there is syphilitic disease involving the aortic valve *only* or *rheumatic disease involving* either the aortic valve only or both the aortic and mitral valves cannot be made by auscultation alone The *presence of chronic auricular fibrillation constitutes* almost conclusive evidence that the lesion is rheumatic as does the presence of peripheral signs of *aortic stenosis or x ray evidence of* compression of the esophagus by an enlarged left atrium In the absence of such differential points the distinction *between syphilitic and rheumatic disease* has to be made on the basis of the history the serologic re*actions etc*

Clinical Course The clinical course of syphilitic aortic insufficiency is often rather rapid once symp*toms have begun to develop Many persons with this* disease develop acute left sided heart failure soon followed by evidence of right sided failure At first the usual methods of management for congestive failure are effective but within a year or two intractable heart failure tends to supervene The prognosis is not so grave as this in all instances but *in the majority of patients* the length of time from the onset of evidence of diminished cardiac reserve to intractable failure and death is shorter *than in most of the other types of chronic heart* disease

Management The management of syphilitic aortic insufficiency is similar in most respects to the management of congestive heart failure in general as discussed in Chap 226 Once heart failure has developed the value of antisyphilitic therapy is dubious

Coronary Ostial Stenosis as the Result of Syphilis. This condition is especially frequent when the coronary arteries take their origin *somewhat distal to* the usual site and slightly above the sinus of Valsalva In the chronic form which develops slowly the *condition may produce no symptoms if the* collateral circulation is adequate However the picture may be that of angina pectoris in a relatively *young patient with syphilis of unexplained* rapidly progressive congestive failure of syncopal attacks (rarely) or a combination of these states The acute *form occurs as the result of sudden* swelling of the aortic wall leading to partial or complete occlusion of one of the coronary ostiums as a manifestation *of the Herxheimer reaction* which occurs when a previously untreated patient with tertiary syphilis is administered a strongly spirochetocidal drug *Here the picture tends to resemble that of myocar*dial infarction and the condition can be fatal within a few days The prevention of such reactions is *discussed with the treatment of syphilitic aortitis* (Chaps 153 and 229)

THYROTOXICOSIS

Thyrotoxicosis of itself does not cause angina pectoris but when it occurs in an individual with coronary arteriosclerosis the increased oxygen needs of the heart may precipitate this disorder Thyrotoxicosis may also lead to congestive failure This complication is uncommon before the age of *forty* and usually occurs in individuals who already suffer from some other form of heart disease although occasionally congestive failure *may appear in per*sons who after cure of the hyperthyroidism present no recognizable cardiac abnormalities In some

older patients the characteristic features of thyrotoxicosis may continue to be so conspicuous even after the development of congestive failure that the diagnosis is simple However in other individuals the recognition of the underlying thyrotoxicosis as the cause of the heart failure may not be made so readily The eye phenomena and the enlargement of the thyroid gland may not be present but these difficulties are not peculiar to the problem of conjoined cardiac failure When in addition the tachycardia is reasonably attributable to the condition of the heart the increased appetite is diminished by the passive congestion of the viscera the loss of weight obscured by the gain due to edema and the warmth and flushing of the skin and the sensitivity to heat modified by the antagonistic effects of cardiac failure it is not surprising that the basic overactivity of the thyroid is hardly discernible

Despite these difficulties thyrotoxicosis should nevertheless be recognized or suspected as an underlying etiologic factor in patients with cardiac disease when any of the following phenomena occur persistent tachycardia that endures after prolonged rest attacks of paroxysmal auricular fibrillation especially in the absence of mitral disease auricular fibrillation in which the ventricular rate is resistant to the slowing effect of full doses of digitalis high output failure in the absence of any other recognizable cause

Even when thyrotoxicosis is suspected as the cause of congestive heart failure the firm establishment of the diagnosis is confronted with additional difficulties Measurement of the basal metabolic rate becomes unreliable in the presence of heart failure which in itself tends to bring about an increase in oxygen consumption because of the increased respiratory effort incident to dyspnea Hence in a patient with heart failure a moderate increase in the basal metabolic rate (up to +25 to +30 per cent) cannot be taken as proof of the existence of overactivity of the thyroid In such cases of heart failure where the role of thyrotoxicosis is in doubt determination of the level of the protein bound iodine or of the rate of uptake of radioiodine may be decisive These procedures may occasionally lead to the detection of thyrotoxic heart disease even when the basal metabolic rate is within normal limits Another important clinical method of establishing the presence of thyrotoxicosis in such cases is the favorable response to the administration of iodine or one of the antithyroid compounds

The treatment of thyrotoxic cardiac disease is essentially a combination of the management of thyrotoxicosis (Chap 64) and that of heart failure as will be discussed later

THIAMINE DEFICIENCY (Beriberi Heart Disease)

A careful history as regards dietary habits and alcoholism should be obtained from all patients with congestive heart failure Elderly males who live alone are particularly likely to have dietary deficiency states

The classic full blown picture of beriberi heart failure is characterized by cardiac dilatation passive congestion and the presence of high output failure Various nonspecific electrocardiographic changes may be present When these findings occur in an individual who gives a history of prolonged dietary insufficiency and who presents other manifestations of vitamin or other nutritional defects and in whom no other cause for the heart failure can be ascertained and when digitalis confers no benefit whereas thiamine brings about a dramatic response the heart becoming smaller and the congestive phenomena disappearing the diagnosis may be considered to be clearly established However not all cases conform completely to this pattern Probably the most important deviation lies in the response to thiamine Not all patients respond quickly spectacularly and completely to the administration of this vitamin In some the improvement takes place slowly over the course of several weeks in others an apparent cure may be followed by recurrent bouts of congestive failure indicating that in them the vitamin deficiency has culminated in irreversible changes in the myocardium that have permanently impaired its efficiency In the favorable cases enlargement of the heart and nonspecific electrocardiographic changes disappear

Clinical and experimental evidence indicates that cardiac involvement is more likely to develop when partial rather than complete thiamine deficiency has been present for a long period of time when the individual has participated in prolonged strenuous labor and when the metabolism and carbohydrate intake have been elevated thus increasing the thiamine requirement

In the United States primary thiamine deficiency is an uncommon cause of congestive failure nevertheless in an individual suffering from myocardial failure the possibility of beriberi heart disease should be considered when the diet has been grossly defective Thiamine deficiency should also be considered as a possible contributing factor in patients with any of the more common primary causes of congestive failure when there is reason to believe that anorexia has been responsible for an inadequate diet Hence all patients with congestive failure whose response to the usual measures is unsatisfactory should be given a trial with thiamine therapy this is especially important in the case of hyperthyroidism

ANEMIA

In many patients with the commoner types of heart disease anemia as the result of intercurrent disorders constitutes an important aggravating factor However severe anemia may in itself produce congestive failure especially in elderly patients

In chronic anemia when the hemoglobin falls to 7 Gm or less tissue hypoxia leads to a decline in peripheral resistance and this in turn may cause a rise in cardiac output and tachycardia At the same time coronary flow may increase as the oxygen content of the blood decreases It is the continued effect of the sustained increase in cardiac output and the inability of the coronary bed to expand beyond a certain limit in the effort to augment adequately the supply of impoverished blood to the myocardium that is responsible for the cardiac dilatation and ultimate failure in some instances of severe anemia Failure is especially likely to occur when cardiac reserve is already compromised either by the involutionary changes of age or by concomitant heart disease

The clinical picture is that of high-output failure with anemia Exact diagnosis may be difficult because severe anemia alone may cause loud systolic murmurs and less commonly diastolic murmurs thus mimicking the features of organic valvular damage This is particularly true in patients with sickle-cell anemia in whom the associated fever and joint pains may lead to confusion with acute rheumatic fever

There are other patients with severe anemia who display failure without tachycardia or the clinical signs of increased cardiac output The reasons for the absence of these compensatory mechanisms are unknown

In patients with heart failure due to anemia digitalis is relatively ineffective treatment consists essentially of the other usual means of managing congestive heart failure plus the treatment of anemia, which naturally depends on the cause Because of the risk of intensifying the congestive failure transfusions of whole blood are generally avoided When myocardial failure and anemia are severe erythrocytes free from plasma, may be administered in small daily doses In less urgent cases management of the anemia alone ill permit a gradual readjustment of the coronary bed to the increasing blood volume

Anemia may also be responsible for the appearance of angina in a person with subclinical coronary sclerosis or it may aggravate an already existent angina This is because of the inability of the sclerotic arteries to dilate adequately in response to the demands imposed by the anemia

ARTERIOVENOUS FISTULA

Arteriovenous fistula is usually the result of a penetrating injury such as a knife or bullet wound Congenital fistulas usually multiple also occur

Pathologic Physiology The initial effect of the leakage is a diminution of effective blood volume by the amount of blood that leads into and is sequestered in the involved extremity The fall in blood pressure leads to an increase in heart rate and a generalized vasoconstriction Nevertheless despite the peripheral vasoconstriction the total peripheral resistance is diminished because of the predominant effect of the leakage Renal vasoconstriction causes a fall in glomerular filtration rate and this plus increased tubular sodium reabsorption leads to an increased blood volume Cardiac output increases and this must be attributed in part or chiefly to the moderate tachycardia and to the increased stroke volume (increased systolic emptying against a lowered peripheral resistance) The heart enlarges long before myocardial failure supervenes—this must imply an increased diastolic volume and at least a slight increase in filling pressure even though right atrial pressure remains within a normal range If these assumptions are correct a third factor contributing to the increased cardiac output may be postulated Eventually the heart fails when the myocardium is incapable of coping with the burden of the sustained elevation of cardiac output

Symptoms and Diagnosis The diagnosis of arteriovenous fistula is not difficult if one keeps the possibilities in mind The swelling and increased warmth in the vicinity of the fistula the continuous murmur with systolic accentuation usually associated with a thrill the enlargement of the heart with the bounding pulse the slowing of the heart when the fistula is compressed (Branham s sign) constitute a characteristic clinical picture When myocardial failure develops the features are those of the high output type Even if an arteriovenous fistula is not immediately apparent, cardiac failure with outspoken peripheral signs of aortic insufficiency without the murmur of that lesion should lead to a careful inquiry into possible previous injuries and wounds and the search for a fistula Since extensive Paget s disease leads to heart failure on essentially the same basis—the development of innumerable AV fistulas in the abnormal bone—it should also be borne in mind under these circumstances

Pulmonary arteriovenous fistulas are rare and practically always congenital probably representing one variant of hereditary telangiectasis The clinical pattern resembles that of the cyanotic types of congenital heart disease and is characterized by cyanosis clubbing of fingers and polycythemia with negative cardiac findings Systolic or continuous

murmurs may be audible over the lungs Hemoptysis is common The diagnosis is confirmed by x ray demonstration of rounded or lobulated pulsating shadows In doubtful cases angiocardiographic studies are definitive

Successful surgical removal of the fistula nearly always leads to dramatic improvement and ultimate disappearance of the manifestations referable to the heart

PRIMARY RETENTION OF SODIUM

Retention of sodium plays an important role in all forms of congestive heart failure regardless of the cause In relatively rare instances acute sodium retention may be a primary cause of cardiac failure Whether sodium retention and the subsequent increase in plasma volume is the cause or the result of the heart failure that frequently complicates acute nephritis is not yet clear and the same is true of the heart failure resulting from the excessive administration of desoxycorticosterone acetate Under these conditions the blood pressure increases rapidly and at the same time the clinical features of increased cardiac output make their appearance

MYXEDEMA

This disorder may affect the heart in a number of different ways First the associated hypercholesteremia favors the development of coronary arteriosclerosis and angina pectoris Second myxedema may be complicated by pericardial effusion which develops slowly and rarely if ever causes tamponade The usual signs of effusion may be lacking Finally myxedema may produce electrocardiographic changes with lowered voltage of all the waves Actual myocardial failure due to myxedema occurs rarely if ever

Among the cardiac findings which should lead to a suspicion of myxedema as a possible cause of the cardiac manifestations are bradycardia despite marked enlargement of the cardiac silhouette low voltage of all waves in the electrocardiogram and dramatic decrease of the cardiac size upon the administration of desiccated thyroid gland Since coronary and cerebral arteriosclerosis are common in persons with myxedema either anginal attacks or psychic disorders may be induced by rapid elevation of metabolic rate Hence thyroid should be administered with great caution

MYOCARDITIS

Formerly many conditions of noninflammatory nature including enlargement secondary to hypertension or to valve lesions and senile myocardial degeneration were grouped together under the term *chronic myocarditis* A reaction against such terminology led to an almost complete abandonment of the term *myocarditis* as a diagnosis but in recent years with a better recognition of its limitations the term is again and more properly being used

Acute myocarditis with pronounced clinical manifestations may be due to rheumatic fever diphtheria collagen disease or scrub typhus Almost any acute infectious process may cause inflammatory changes in the myocardium but clinically significant findings are rare The diagnosis is justified when evidence of heart disease and more especially gallop rhythm increase in size conduction defects and other electrocardiographic changes set in during or following acute infection Except for the types complicating rheumatic fever and diphtheria the prognosis is good and in the rare instance of fatal circulatory collapse it is difficult to estimate the respective roles of the myocarditis and of the virulence of the infection Diphtheritic myocarditis commonly is fatal when it is sufficiently severe to produce clinical manifestations In the milder instances with slight electrocardiographic and no clinical manifestations complete recovery occurs Although immediate recovery from rheumatic myocarditis usually takes place long term impairment of the heart is the rule The management is that of the underlying disease process plus that of congestive failure when this complication supervenes Digitalis rarely has a dramatically beneficial effect on any type of acute myocarditis

Chronic myocarditis may be of known or unknown cause The known causes include such rare disorders as tuberculous myocarditis and trichinosis of the myocardium When a more or less diffuse inflammatory lesion of unknown etiology is confined to the myocardium all other evidences of a related infection or other disorder being absent the condition is designated as *isolated* or *Fiedler's* myocarditis rarely recognized during life

TRAUMATIC HEART DISEASE

Cardiac damage may be due to both penetrating and nonpenetrating injuries to the heart the most frequent cause of the latter being the automobile accident though any heavy blow to the chest wall may be responsible Serious injury of the heart may ensue though there is no external sign of bruise Any structure of the heart may be affected (see Fig 161 Chap 223)

The valve cusps may be torn usually the mitral or aortic and the appearance of a loud murmur in a previously healthy person is followed by rapidly progressive myocardial failure A coronary artery may be injured and myocardial infarction may ensue or the same clinical picture may follow severe myocardial contusion in both instances character

istic alterations in the ventricular complexes of the electrocardiogram are displayed Various disturbances of the heart rhythm may be seen the authors have encountered at least two cases of bundle block presumably incurred as a result of boxing, and complete AV block has been reported Hemorrhage into the pericardium with tamponade may follow a tear of the myocardium or of the pericardial vessels or of a coronary branch Obliteration of the pericardial sac may follow pericardial hemorrhage and the electrocardiogram may reveal permanently inverted T waves

Treatment for myocardial failure due to rupture of the valves is hardly ever effective If the symptoms are those of infarction it is impossible to distinguish between contusion and coronary artery injury in any case the treatment is the same and is that accorded the patient with infarction Pericardial tamponade has been managed successfully by repeated taps alone Other investigators advocate immediate surgical intervention or intervention if tamponade recurs after two taps

MALIGNANT CARCINOID (Argentaffinoma)

The clinical picture associated with malignant carcinoid is characterized by episodic flushing cyanosis telangiectasia of face and the frequent though not constant involvement of the right heart when liver metastases are present Pulmonic stenosis with tricuspid insufficiency leads to right ventricular hypertrophy and finally failure with systemic venous engorgement It is believed that these various cardiovascular manifestations are due to the excessive quantities of serotonin (5-hydroxytryptamine) released into the circulation by the primary tumor and liver metastases It has been believed but not proved that the right heart lesions are part of a widespread connective tissue disorder the left heart being spared because serotonin is destroyed in its passage through the lung

The combination of pulmonic stenosis and cyanosis brings up the possibility of confusion with congenital pulmonic stenosis with a patent foramen ovale In the latter case the cyanosis with polycythemia is due to a right left shunt causing arterial hypoxemia In the former abnormal arterial oxygen unsaturation is absent the cyanosis without polycythemia being due to alterations in the cutaneous vasculature

HEART DISEASE OF OBSCURE ETIOLOGY

Obscure etiology is meant here to imply that a form of heart disease is encountered that does not appear to belong to any of the more common categories previously described In some of these cases continued observation may reveal a hitherto unrecognized structural lesion such as aortic stenosis or a mitral valve defect An unexpectedly poor response to therapy or the manifestations of high output failure may lead to the discovery of marked thyrotoxicosis In still others autopsy examination may disclose previously undetected lesions such as a relatively common type of congenital heart disease or the scars of healed infarcts or a valvular lesion In other words many cases of obscure etiology are simply unrecognized examples of common heart disease Nevertheless even if one gives thoughtful consideration to this reminder one is forced at times by one or another puzzling clinical feature of heart disease to speculate on the possibility that an unusual type of heart disease may actually be present Frequently the problem revolves about the patient without apparently significant murmurs or pulmonary disease or hypertension or clear cut coronary disease (anginal pain myocardial infarction)

When this situation arises in an elderly person it is hardly ever considered a problem since this type of case almost by definition is labeled arteriosclerotic heart disease However it has been pointed out previously that the absence of an obvious etiologic factor does not *ipso facto* justify the diagnosis of arteriosclerotic cardiac disease in an elderly patient without anginal pain because the same problem arises in young adults and even in children The following are some of the more unusual forms of heart disease to be considered

Endocardial Fibroelastosis This disorder occurs most frequently in infants but adults of all ages may be afflicted At autopsy the findings are identical in both marked cardiac hypertrophy more or less generalized thickening of the endocardium chiefly of the left ventricle and frequently mural thrombi The clinical picture is that of gradual or rapidly progressive heart failure occasionally typical angina pectoris systolic murmurs that seem inadequate to account for the considerable enlargement of the heart frequent episodes of systemic embolization irregularities of rhythm and nonspecific electrocardiographic abnormalities In the older person particularly when angina is present differentiation of this disease from coronary sclerosis is difficult if not impossible In younger patients under forty the disorder may be suspected when the clinical picture fails to conform with one of the common causes of heart disease at that age and when repeated arterial embolization occurs The cause is unknown but in infants at least the best explanation appears to be intrauterine hypoxia due to premature closure of the foramen primum or foramen ovale

An identical clinical picture with *endocardial fibrosis and subendocardial necrosis* has been described as occurring frequently in certain African

tribes. In some of these patients there is evidence that nutritional deficiencies are at least partially responsible; in others there is no clear cut relationship to nutritional disorder. What connection their illness has with a practically identical one occurring in this country, usually designated as *idiopathic hypertrophy of the heart*, is not clear. In idiopathic hypertrophy of the heart many patients give a history of long standing alcoholism and inadequate diet, but no specific nutritional defect has been proved. The term *cardiovascular collagenosis* has been applied to this group because of the histologic demonstration of degeneration of collagen fibers and of the associated ground and cement substances.

The recognition of cardiac involvement by *sarcoidosis, scleroderma, hemachromatosis or amyloid disease* will depend on the demonstration of these disorders elsewhere in the body by biopsy or other precise methods. The same would be true of the other well defined *collagen diseases*. Pericarditis is so common in disseminated lupus and occasionally in periarteritis nodosa that these diseases must be considered when pericarditis of uncertain origin is encountered. Scleroderma and amyloid disease may present a picture identical with that of constrictive pericarditis.

Neoplasms of the Heart. With the exception of myxoma of the left atrium, primary tumors of the heart (rhabdomyoma, mesothelioma of the pericardium, a variety of other benign tumors or their malignant counterparts) are medical curiosities. *Myxoma of the atrium*, usually of the left, is also rare but presents a more distinctive clinical picture and the possibility of surgical cure. This condition should not really be considered in a discussion of heart disease of obscure origin because almost invariably myxoma is diagnosed as mitral stenosis and recognized at operation. Myxomas of the atrium may display the characteristic features of ball valve thrombus: variability of the murmurs of mitral stenosis with change of position, syncope, paroxysms of acute pulmonary edema—all due to sudden and intermittent obstruction of the mitral orifice.

Table 113 CHIEF CLINICAL FEATURES OF SOME OF THE RARER CARDIAC DISORDERS *

Etiologic group	Specific disorder	Important clinical features: Cardiac	Important clinical features: Noncardiac	Accessory features	Remarks
Infectious	Scrub typhus	Enlargement Gallop	Eschar, fever	ECG nonspecific changes	Orient and tropics
	Diphtheria	Arrhythmias Failure	Nasopharyngitis Ulcers of skin	Kleb-Loeffler bacillus	Grave prognosis
	Chagas disease	Enlargement	Anemia Debility	Antibodies to *Trypanosoma cruzi*	Sudden death frequent
	Trichinosis	Enlargement	Muscle pains	Eosinophilia	Ingestion of raw pork
Metabolic	Xanthomatosis	Angina pectoris	Xanthomas Xanthelasma	Hypercholesteremia	Family history
	Von Gierke's disease	Enlargement	Enlarged liver	Hypoglycemia	Infants
	Cardiac amyloidosis	Enlargement Failure	Often none	Congo red test of no value	Other features of amyloidosis may be absent
Therapeutic	Excessive intravenous fluids	Dilatation Failure	Evidence of the primary disease	Hemodilution	Especially elderly persons
	Emetine	Tachycardia Hypotension	Evidence of the primary disease	T wave inversion	
	Desoxycorticosterone	Enlargement	Hypertension Edema	Hemodilution	
Miscellaneous	Acute nephritis	Enlargement Gallop	Hypertension Edema	Hematuria Proteinuria	
	Polyarteritis	Enlargement Pericarditis	Fever Arthritis	Leukocytosis Eosinophilia	Bizarre clinical picture
	Libman-Sacks disease	Enlargement Pericarditis	Fever, arthritis, lupus of face	Leukopenia	Young females, atypical verrucous endocarditis
	Post partum heart failure	Enlargement Failure	Recent delivery		
	Myocardial sarcoidosis	Enlargement Failure	Enlarged spleen, liver, nodes	Hilar shadows Bone lesions Increased globulin	Slight fever, cutaneous lesions

* The list is not comprehensive, as many disorders are omitted. None of the types due to curable causes are listed since they have been considered in the text.

Secondary tumors of the heart are much more frequent and have been described as occurring in 10 to 20 per cent of cases of malignancy The most common form is by direct extension to the pericardium of a primary carcinoma of the breast or bronchus malignant thymoma or lymphoma The clinical picture is usually that of rapidly recurring pericardial effusion often bloody Metastases to the myocardium are rarely responsible for symptoms or signs that permit recognition although suspicion should be aroused when the development of intractable failure or of a distinctly abnormal electrocardiogram takes place in a person known to harbor other metastatic lesions and previously free of heart disease

There is a logic in the diagnosis of a rare cardiac disorder such as pericardial disease in the presence of known malignant disease of the mediastinum or sarcoid heart disease when sarcoidosis has been demonstrated elsewhere in the body One should bear in mind however that the diagnosis of many of these conditions can hardly be anything other than a lucky guess often the artificial by product of the "C P C" atmosphere and that a lengthy and detailed differentiation can only be a tale full of sound and fury signifying nothing

Geographic factors are sometimes of importance in determining the cause of heart failure of obscure origin Residence in areas where *Schistosomiasis mansoni* is endemic should bring to mind the possibility that this disease may cause cor pulmonale while cardiac trypanosomiasis (Chagas disease) should be considered in persons living in northern and central South America In the Orient heart failure is sometimes due to scrub typhus

Since cure or significant amelioration of certain forms of heart disease is now possible they must always be borne in mind when an obscure form of heart disease is encountered Thus one should search carefully for bacterial endocarditis the various causes of high output failure certain types of congenital heart disease constrictive pericarditis and cor pulmonale due to thromboembolic disease

Some of the pertinent features of a few of the many rarer cardiac disorders are summarized in Table 113

PERICARDITIS

Pericarditis may be classified according to two different methods both of practical importance

I Etiologic and prognostic classification
  A Infectious
    1 Mild (benign pericarditis)
    2 Grave (including rheumatic tuberculous and pyogenic)
  B Noninfectious
    1 Uremic (prognosis usually grave)
    2 Ischemic (myocardial infarction)
    3 Neoplastic (rare)
  C Uncertain etiology
    1 Polyarteritis
    2 Disseminated lupus erythematosus
II Morphologic and clinical classification
  A Acute
    1 Fibrinous (without significant effusion)
    2 Serofibrinous (with significant effusion)
  B Chronic
    1 Constrictive (usually due to tuberculous or pyogenic infection or to collagen disease)
    2 Adhesive mediastinopericarditis (usually rheumatic)

General Comments Pain is usually indicative of an infectious type of pericarditis but this is a rule to which there are frequent exceptions Pain may be absent in a slowly developing tuberculous pericarditis and it may occur occasionally in the pericarditis of disseminated lupus or renal failure although in the latter it is rarely a prominent symptom probably because of the stuporous or comatose state of the patient Postinfarctional pericarditis is practically always painless nevertheless the characteristic pleuritic type of pain of the infectious type may be encountered rarely when there is no other evidence of infection Moreover the sudden development of hemopericardium especially following the administration of anticoagulants may be associated with severe pain

Pericarditis causes three distinct types of pain By far the most common is the pleuritic variety related to respiratory movements and always aggravated by deep inspiration or cough This type of pain is due to the pleuritic component of the pleuropericarditis so commonly present in the infectious forms It may be felt in the region of the left border of the heart or the upper abdomen or back (intercostal nerve involvement) or it may be experienced at the left shoulder and trapezius ridge (phrenic nerve involvement) The next most common pericardial pain is the steady crushing substernal pain identical with that of acute myocardial infarction if the pleuritic pain is absent differentiation on the basis of the pain alone is impossible The third type of pericardial pain one that a priori should appear to be the most common and characteristic is actually quite uncommon this pain is synchronous with the heart beat and is felt at the left border of the heart and left shoulder Rarely all three types may be present simultaneously

The *pericardial friction rub* is the most important physical sign sometimes elicited only when firm pressure with the stethoscope is applied to the chest

tribes. In some of these patients there is evidence that nutritional deficiencies are at least partially responsible; in others there is no clear-cut relationship to nutritional disorder. What connection their illness has with a practically identical one occurring in this country, usually designated as *idiopathic hypertrophy of the heart*, is not clear. In idiopathic hypertrophy of the heart many patients give a history of long-standing alcoholism and inadequate diet, but no specific nutritional defect has been proved. The term *cardiovascular collagenosis* has been applied to this group because of the histologic demonstration of degeneration of collagen fibers and of the associated ground and cement substances.

The recognition of cardiac involvement by *sarcoidosis, scleroderma, hemachromatosis, or amyloid disease* will depend on the demonstration of these disorders elsewhere in the body by biopsy or other precise methods. The same would be true of the other well-defined *collagen diseases*. Pericarditis is so common in disseminated lupus and occasionally in periarteritis nodosa that these diseases must be considered when pericarditis of uncertain origin is encountered. Scleroderma and amyloid disease may present a picture identical with that of constrictive pericarditis.

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proach to the pericardium the authors prefer the one just lateral to the apex When pericardial effusion recurs rapidly and frequently a pleuropericardial window may be established If pericardial effusion is of obscure origin and long duration exploration is justifiable for the purpose of establishing etiology and of instituting specific therapy

Acute Benign Infectious Pericarditis

This disorder is an important clinical entity because of its frequency and because it may be confused with other more serious affections It is presumed to be due to a viral infection but this is unproved It occurs at all ages but most commonly in young adults Often there is a history of an antecedent respiratory infection within the preceding 2 or 3 weeks Fever and pericardial pain appear at about the same time an important feature in the differentiation from myocardial infarction Fever and other constitutional symptoms are usually mild to moderate but occasionally the initial symptoms are stormy with fever rising to 104 to 105 F The disease ordinarily runs its course in a few days to 2 weeks Tamponade is exceptional and subsequent constrictive pericarditis is very rare As is true in other forms of acute pericarditis the pain is usually aggravated by breathing change of position or swallowing The T wave alterations in the electrocardiogram may persist for several years or indefinitely constituting a subsequent source of confusion in persons without a clear history of pericarditis It is possible that some such infection may be the explanation of the soldiers patch a localized thickening of the visceral pericardium sometimes observed at autopsy Since there is no specific test for the disorder the diagnosis is primarily one of exclusion The important points to keep in mind are to avoid the error of considering the illness to be due to myocardial infarction when the predominant symptom is a steady unwavering substernal pain and also to avoid disregarding the possibility of other more serious causes such as disseminated lupus or tuberculosis simply because the initial course is mild In most cases neither the tetracyclines nor any other specific form of therapy has any value

Other Types of Infectious Pericarditis

The more serious and common forms include those due to rheumatic fever tuberculosis and pyogenic infections The *rheumatic type* is practically always associated with other evidences of severe carditis and usually preceded or followed by valvular damage Pericardial effusion sometimes responds favorably to salicylates even though the carditis is otherwise uninfluenced

Tuberculous pericarditis occurs most commonly over the age of forty and usually in an individual with obvious pulmonary pleural or peritoneal tuberculosis but also when evidence of tuberculosis elsewhere is absent The infection probably reaches the pericardium by direct extension from the mediastinal lymph nodes and it commonly terminates in constrictive pericarditis The clinical picture may vary from one that resembles acute benign infectious pericarditis to one without a history of pain the symptoms being those of infection in an individual with massive effusion with or without manifestations of tuberculous involvement of other structures It is important to bear this condition in mind when a middle aged or elderly person with fever presents signs of pericarditis The prognosis was formerly very grave 90 per cent dying within a few months one important factor being the frequency of miliary tuberculosis With the newer antimicrobial drugs the mortality has been very much reduced The initial management of tuberculous pericarditis is that of tuberculosis in general with vigorous use of the newer drugs (p 933) In addition the usual measures to combat cardiac ascites and edema (p 1313) may be necessary Constrictive pericarditis develops in most instances and calls for surgical therapy after the active process has been controlled

Purulent pericarditis is now far less common than before the advent of effective antibiotics particularly for the treatment of pneumonia Once pyogenic pericarditis has been recognized surgical intervention should be undertaken unless antibiotic therapy is rapidly effective

Noninfectious Pericarditis

The two most common causes of noninfectious pericarditis are uremia and myocardial infarction In both instances the involvement of the pericardium is a relatively unimportant feature except in the occasional case of postinfarctional hemorrhagic pericarditis due to anticoagulant therapy This latter should be kept in mind when the patient with an acute infarction develops recurrent chest pain and evidence of pericardial effusion in which case cessation of anticoagulants administration of vitamin K_1 oxide (Mephyton) and possibly pericardial tap may be of crucial importance

Neoplastic pericarditis occasionally occurs as the result of invasion of the pericardium by malignant tumors of adjacent structures The condition is rare and has little practical importance

Pericarditis Due to Collagen Disease The most important is that due to disseminated lupus in which disease it occurs at some time in its course in over 50 per cent of the cases Often it appears as an asymptomatic effusion at other times pain is present and very rarely tamponade may develop When it occurs in the absence of other evidences of the underlying disorder differentiation from

wall The pericardial rub is likely to be inconstant and transitory and a loud to and fro leathery sound may disappear within a few hours possibly to re appear the following day The electrocardiogram usually displays elevation of the S T segments in several leads without reciprocal depressions in others or significant changes in the QRS complex Later the T waves become inverted and in some instances this latter change is permanent

When an effusion develops the fluid nearly always has the physical characteristics of an exudate Bloody fluid is most commonly due to tuberculosis or tumor but it may also be found in the pericarditis of rheumatic fever uremia the acute benign infectious form and of course in the hemopericardium following infarction

Tamponade When fluid in the pericardium accumulates in an amount sufficient to cause serious obstruction to the inflow of blood to the ventricles *tamponade* is said to be present The amount of fluid necessary to produce this critical state may be as small as 250 to 300 ml when the fluid develops rapidly or it may be over 1 000 ml in slowly developing effusions when the pericardium has had the opportunity to stretch and adapt to the increasing fluid Tamponade is usually due to tuberculosis pyogenic infection or tumor but it may occur in rheumatic fever acute benign pericarditis disseminated lupus erythematosus or postinfarctional hemopericardium The symptoms are primarily due to the sudden fall in cardiac output and systemic congestive failure Orthopnea with little or no pulmonary congestion is also prominent the mechanism of this dyspnea is not understood The physical signs are the increase in the contour of the heart especially important when this has occurred under observation increasing heart rate and falling blood pressure with narrowed pulse pressure distention of the neck veins and rapid enlargement of the liver The heart sounds tend to become faint but they may remain loud the friction rub may disappear or remain clearly audible the apex beat may disappear but sometimes is felt well within the left border The distention of the neck veins is increased during inspiration or when pressure is applied with the palm of the hand over the liver (hepatojugular reflex) This phenomenon is due to the inability of the right ventricle to accommodate the increased inflow of blood and the consequent reflux of blood into veins already under increased tension A protodiastolic gallop is often heard Very important is the appearance of a distinctly percussible right border of the heart extending more than 5 cm from the midline On fluoroscopic examination the ventricular pulsations are usually diminished or absent

One of the most important clues is the *paradoxic pulse* best demonstrated by taking the blood pressure in expiration and inspiration a difference of 10 mm Hg or more being considered a positive test The mechanism of the paradoxic pulse is still uncertain It occurs not only in pericardial effusion with tamponade and constrictive pericarditis but also in various conditions associated with bronchial obstruction and in severe congestive failure with peripheral vascular collapse The probable explanation for the phenomenon is that it represents an exaggeration of the normal disproportion between right ventricular output and the capacity of the pulmonary vascular bed during inspiration Normally during inspiration the fall in intrathoracic pressure causes increased filling of the right ventricle because of the increased gradient of pressure between the extrathoracic veins and the right chambers of the heart The left ventricle which draws blood from intrathoracic structures is relatively unaffected Right ventricular output increases but at the same time the pulmonary vascular bed is increased disproportionately the net result being a diminished flow to the left side of the heart and a corresponding reduction in left ventricular output In cardiac tamponade flow into the right ventricle is impeded and right ventricular output is small and fixed However the inspiratory enlargement of the pulmonary vascular bed is relatively uninfluenced and the normal slight reduction of flow into the left side of the heart is exaggerated It is the corresponding drop in left ventricular output that is responsible for the inspiratory fall in blood pressure

X ray findings are often inconclusive and there is no one configuration that is constant and pathognomonic *A large cardiac shadow with complete absence of visible pulsations associated with absence of pulmonary congestion is more convincing evidence of pericardial effusion* In some instances angiocardiography has provided decisive proof of the existence of pericardial effusion

One should not be misled into an incorrect diagnosis of pneumonia by signs of consolidation of the left lower lobe as these are not infrequent in the presence of massive pericardial effusion (Ewart s sign) It is also important to bear in mind that differentiation between cardiac tamponade and severe myocardial failure may sometimes be exceedingly difficult The decision is a matter of great practical importance because digitalis has no beneficial effect in instances of cardiac tamponade while lessening of the intrapericardial pressure by pericardial tap may be lifesaving

Treatment Patients with pericarditis should be observed with care and if signs of effusion develop the blood pressure and heart rate should be recorded at hourly intervals If the symptoms and signs of tamponade appear pericardial paracentesis should be instituted at once since relief of pressure may be lifesaving Of the various methods of ap

pericardial paracentesis Thus the diagnosis of con strictive epicarditis is made when the removal of a large amount of fluid from the pericardial sac fails to cause a sharp decline in the previously elevated venous pressure Operative treatment is especially effective in patients with this condition

Chronic Adhesive Mediastinopericarditis This condition is an exceedingly rare result of rheumatic infection the heart being bound to the surrounding structures by dense adhesions The condition is almost invariably associated with rheumatic lesions of the mitral valve Diagnosis depends mainly on the demonstration of Broadbent s sign systolic re traction of the posterior left lower interspaces but since the same phenomenon may be witnessed whenever the heart is greatly enlarged it must be concluded that diagnosis of the condition is at best uncertain and probably impossible Favorable re sults have been reported in a few instances follow ing removal of the ribs in the precordial and left axillary regions in order to allow the heart to pull against soft tissue rather than bone

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acute benign infectious pericarditis or a mild form of tuberculous pericarditis may be made only on discovery of L E cells Pericarditis due to periarteritis is rarely of significance

Chronic Pericarditis

Constrictive Pericarditis This disorder results when the healing of acute fibrinous or serofibrinous pericarditis results in obliteration of the cavity of the sac with the formation of granulation tissue which gradually contracts forming a firm scar encasing the heart and interfering with filling The condition is usually the result of tuberculous staphylococcal or pneumococcal infection but less commonly other organisms or collagen disease may produce it The clinical picture is characterized by dyspnea on exertion which however is often relatively slight at rest while orthopnea may be entirely absent pronounced enlargement of the liver distention of the cervical veins ascites and peripheral edema The heart is normal in size in about half the cases in the others it is slightly to markedly enlarged A paradoxic pulse is frequently encountered and a protodiastolic gallop is present in most patients Both by palpation and by x ray marked diminution in cardiac pulsation is noted A very important finding is the presence of calcification of the pericardium visible by x ray in about one half the cases The spleen is sometimes palpable and in the absence of evidence of bacterial endocarditis splenomegaly in a patient with congestive heart failure should arouse suspicion of constrictive pericarditis The electrocardiogram frequently displays low voltage and flattening or inversion of the T waves in all three limb leads Auricular fibrillation is often present in this condition

Congestive failure is initially the result of tamponade with impairment of filling of both ventricles However the fibrotic process may extend into the myocardium and congestive failure may be due to the combined effects of the myocardial and the pericardial lesions The interference with filling reduces the work of the heart and myocardial atrophy may occur This probably accounts for the delayed beneficial effects of operative treatment Improvement may not become apparent until a number of months have elapsed Presumably the atrophy disappears when the impairment of filling is removed by resection of the pericardium Because the filling of the right ventricle is impaired acute pulmonary edema does not occur and orthopnea is minimal Despite the hindrance to left ventricular filling the right ventricle is unable to flood the lungs with blood

Inasmuch as the usual physical signs of cardiac disease (murmurs cardiac enlargement) may be inconspicuous or entirely lacking the presence of hepatic enlargement and intractable ascites may lead to a mistaken diagnosis of cirrhosis of the liver This error should be avoided if the veins of the neck are inspected carefully in all patients with ascites and hepatomegaly *Given a clinical picture resembling cirrhosis but with the added feature of distended cervical veins careful search for calcification of the pericardium by x ray examination and detection of the electrocardiographic signs described above may disclose a curable or remediable form of heart disease that might otherwise be overlooked*

Occasionally constrictive pericarditis will be confused with rare disorders of the endocardium or myocardium which likewise produce disproportionate impairment of filling Thus in a patient presenting the classic features of constrictive pericarditis one should consider the possibilities of constrictive endocarditis (fibroelastosis subendocardial fibrosis) and constrictive myocarditis (scleroderma amyloid disease of the heart healed eosinophilic myocarditis) before advising pericardectomy In the absence of demonstrable calcification of the pericardium or of electrocardiographic changes which are typical of pericarditis it may be impossible to differentiate these conditions from constrictive pericarditis

In the treatment of constrictive pericarditis digitalis is rarely of much value but diuretic drugs and sodium restriction are useful The benefits derived from the delicate operation of cardiac decortication are often striking and frequently the improvement while slight at first is progressive over a period of many months The patient may be restored from a state of invalidism to something approaching normal activity The operation should be performed as soon as the causative infection has become relatively inactive as indicated by the temperature and sedimentation rate in order that the scar tissue will not have become too dense Rarely fluoroscopic examination may reveal calcification of the pericardium in an individual who is free of all symptoms referable to the heart and so long as venous pressure remains normal treatment is unnecessary

Most instances of constrictive pericarditis are of tuberculous origin Streptomycin treatment during the phase of effusion may prevent the development of constriction Preoperative and postoperative administration of streptomycin may prevent spread of tuberculosis Such spread and congestive failure are the usual causes of death

Constrictive Epicarditis (*Porter s Syndrome*) Ordinarily constrictive pericarditis occurs only after fluid has been resorbed from the pericardium and results from fusion and marked thickening of the visceral and parietal layers Rarely the fluid persists and the epicardium becomes rigid but only slightly thickened resembling an egg shell In such instances the signs of tamponade persist despite

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of pulmonic/systemic flow may reach 20 or more In the latter situation however the difference in oxygen saturation between arterial and venous blood is so small that accurate calculation of pulmonary flow by the usual methods of cardiac catheterization is impossible

With left to-right shunts at the atrial or ventricular level, the right ventricle is required to pump an increased volume of blood per minute at pressures which may or may not be higher than normal This results in right ventricular dilatation and hypertrophy the degree of hypertrophy being roughly proportional to the degree and duration of pulmonary hypertension When the shunt is at the level of the pulmonary artery as in patent ductus arteriosus uncomplicated by pulmonary hypertension only the left ventricle hypertrophies when pulmonary hypertension appears right ventricular hypertrophy is superimposed

Left ventricular work is increased if the site of the shunt is in the ventricular septum or distal to the left ventricle Left ventricular hypertrophy and dilatation result but may be overshadowed by simultaneous right ventricular hypertrophy

Arterial unsaturation does not occur with pure left to-right shunts but clinical cyanosis may occasionally be present as a result of decreased systemic flow or inadequate oxygenation in the lung The latter is rare

Auscultatory findings with left to-right shunts depend on the specific malformations When the shunt is distal to the mitral valve an apical mid or late diastolic murmur is often present presumably because the greatly increased blood flow across a normal mitral orifice is equivalent to relative mitral stenosis A similar diastolic murmur is sometimes present in cases of atrial septal defect although its origin is not clear

Right to-left Shunts In this condition systemic venous blood returning to the heart enters the left heart chambers or systemic arterial circuit without passing through the pulmonary capillary bed

The major signs and symptoms accompanying right to-left shunts result not only from the diversion of blood through abnormal pathways but also from the obstruction to blood flow through normal pathways (e g pulmonic stenosis) which is often present The functional effect of these abnormalities is to reduce the partial pressure of oxygen in arterial blood and to burden one or both ventricles with extra work Some of the resulting signs and symptoms are common to many different malformations and will be discussed individually

Cyanosis Cyanosis or the appearance of clinically recognizable blueness in the systemic capillaries is usually a direct result of lowered arterial oxygen saturation Slowed peripheral blood flow and inadequate saturation in the lungs can also cause cyanosis but these factors are of secondary importance in cyanotic congenital heart disease The oxygen saturation of the blood leaving the lungs is usually normal but the admixture of venous blood distal to the site of the right to-left shunt reduces the arterial saturation The degree of arterial unsaturation varies directly with the volume of the venous-arterial shunt and indirectly with the volume of pulmonary blood flow

Cyanosis is best observed in the nail beds buccal mucous membranes and lips It becomes evident clinically only when the equivalent of approximately 5 Gm per cent of unsaturated hemoglobin is present in arterial blood hence patients with anemia may not show clinical cyanosis even though the oxygen saturation of arterial blood is well below normal while polycythemia accentuates cyanosis with even minimal degrees of arterial unsaturation

In congenital heart disease cyanosis usually implies the existence of an abnormal communication between the venous and arterial sides of the circulation which may be a patent foramen ovale defect of the interatrial or interventricular septum transposed great vessels patent ductus arteriosus or other communication between the aorta and pulmonary artery or (rarely) direct entry of systemic veins into the left atrium In addition to the abnormal communication hemodynamic conditions must be such that blood flows through the opening from right to left " producing a venous arterial shunt this usually requires elevation of right atrial, right ventricular or pulmonary artery pressure above normal levels An extreme example of a structural anomaly which produces a right to-left shunt is seen in complete transposition of the great vessels in which the right ventricular outflow enters the aorta instead of the pulmonary artery In occasional cases clinical cyanosis may be due to diminished peripheral flow or other factors as in the normal vigorously crying child It is almost never due to inadequate pulmonary oxygenation

Polycythemia Polycythemia with red cell counts of 6 to 9 million per cubic millimeter and hematocrits as high as 80 develops in response to the lowered arterial oxygen tension The oxygen-carrying capacity of the blood is thereby increased partially compensating for the decreased oxygen saturation When the arterial saturation at rest is 70 per cent or more circulating hemoglobin increases to such an extent that the oxygen content of arterial blood is actually higher than normal

The polycythemia is absolute rather than relative i e the total red cell mass is increased The plasma volume is usually decreased but the red cell volume increase is of such magnitude that total blood volume is greater than normal

This adaptative response is not entirely benefi

225 CONGENITAL HEART DISEASE

William R Milnor and Henry T Bahnson

The demonstration that many congenital malformations of the heart can be treated successfully by surgery has radically changed the physician's approach to congenital heart disease Not long ago the nonspecific clinical diagnosis of *congenital heart disease* or *morbus caeruleus* was regarded as all that was possible or necessary in many cases Today the accurate recognition of specific lesions and a quantitative estimate of the burden they impose on the heart in each case is of great practical importance

The *incidence* of congenital heart disease in the general population is probably in the neighborhood of 0 3 per cent of all live births and congenital malformations constitute from 1 to 5 per cent of all cases of recognized heart disease after infancy

Etiology Many abnormalities of the heart and great vessels can be explained by failure to progress beyond an early stage of embryologic development while others seem to represent aberrant development of a normal structure The cause of these embryologic misadventures is unknown in most cases but various theories involving fetal hypoxia fetal endocarditis immunologic abnormalities vitamin deficiencies and specific genetic abnormalities have been proposed

In some cases a clear relation between maternal rubella during gestation and congenital malformations of the heart has been demonstrated It appears that maternal rubella during the first 2 months of pregnancy will lead to congenital malformations of the heart cataracts deaf mutism or other anomalies in almost all cases The later in gestation the rubella occurs the lower the incidence of congenital abnormalities but cases of congenital heart disease have occurred following rubella in the sixth month of pregnancy

In clinical practice however relatively few cases of congenital heart disease—probably less than 2 per cent—can be attributed to this cause and in most instances no significant environmental factor during fetal development can be elicited by history

Inheritance With few exceptions patients with congenital heart disease have a negative familial history for congenital malformations There are nevertheless well documented exceptions including families in which the same malformation has recurred in two or three successive generations Patent ductus arteriosus is the commonest lesion thus reported but this may simply reflect the relatively benign course of this anomaly

There is good evidence that factors concerned with some congenital abnormalities can be transmitted as mendelian recessive traits while some may arise as a result of *de novo* mutation

In practice the birth of one child with a congenital malformation of the heart does not in itself contraindicate future pregnancies since the risk that subsequent siblings will have congenital malformations is extremely small

The incidence of some congenital malformations of the heart shows clear sex differences which may be attributed to either sex linked inheritance or environmental factors in utero Defects of the atrial septum and persistent patency of the ductus arteriosus are much more common in females than in males pulmonic stenosis and ventricular septal defect show little or no sex difference coarctation of the aorta and congenital aortic stenosis affect males predominantly

PHYSIOLOGIC EFFECTS

Shunts

A cardiovascular shunt may be broadly defined as blood flow through a pathway which diverts a portion of the ventricular output from the pulmonary or systemic capillary beds It requires an open communication (or one potentially open such as a patent foramen ovale) between the pulmonary and systemic circulation the direction of blood flow being determined by the pressures existing on either side of the communicating pathway Such communications usually represent persistence of an embryonic stage of development into postnatal life Since pressures in the left heart and systemic circulation normally exceed those in the corresponding part of the pulmonary circuit shunts are usually from left to right unless the right sided pressures are pathologically increased In some cases changing pressure gradients through the heart cycle will produce shunts which vary in direction In other instances the existence of roughly equivalent pressures on opposite sides of a defect may prevent shunting of blood even though the defect may be large Streamlining of flow appears to be an important factor in some instances and may produce shunting in the absence of measurable pressure gradients

Left to-right Shunts In this situation a portion of the blood which flows through the lungs is diverted before reaching the systemic capillaries and is recirculated through the pulmonary bed The volume of blood pumped through the pulmonary capillaries therefore exceeds the systemic flow per minute unless complicating shunts in the opposite direction are also present Pulmonic blood flows of 10 to 12 liters per minute with systemic flows of 2 to 3 liters per minute are common and the ratio

murs may be as loud as grade 4 but are not usually accompanied by a thrill When the pulmonary artery is greatly dilated there is sometimes an extra sound in early systole ("systolic click")

DIAGNOSTIC METHODS

Roentgenography The importance of roentgenographic examination in congenital heart disease can hardly be overstated Fluoroscopic examination should be carried out in every patient suspected of having a cardiac malformation and full size chest films in the posteroanterior and oblique positions with barium in the esophagus should be recorded The size and position of the great vessels and heart chambers the vascularity of the lung fields and the pulsations observed during fluoroscopy are often the deciding clues in differential diagnosis Characteristic configurations in some congenital anomalies of the heart are shown in Fig 163

Angiocardiography The introduction of radiopaque solutions into the blood stream to demonstrate the course of the blood and to outline the chambers of the heart is often of great help in diagnosis The extent of the information which can be obtained is determined largely by the technical excellence of the equipment used Angiocardiography is most helpful with complex malformations in which data from catheterization are inadequate or equivocal particularly when there is some uncertainty as to how blood reaches the lungs or which ventricle communicates with the systemic circulation

The contrast medium is usually introduced into a peripheral vein although injection directly into the heart through a cardiac catheter ("selective angiocardiography) has been used extensively in some centers Although intracardiac injection gives technically excellent films the associated morbidity and mortality are distinctly higher than with intravenous injection

In planning diagnostic studies on a patient it should be remembered th t the risk of angiocardiography using conventional intravenous injection is appreciably higher than that of right heart catheterization In a joint report by several medical centers in the United States the mortality in a series of 8 000 angiocardiograms was given as 0 3 per cent As with cardiac catheterization the hazard is greatest in the presence of pulmonary hypertension or cyanosis

Electrocardiography In congenital heart disease the principal contribution of electrocardiography is the determination of specific ventricular hypertrophy and it is often more sensitive for this purpose than roentgenography The characteristic changes with right left and combined ventricular hypertrophy are described in Chap 223 Right ventricular hypertrophy and enlargement are common with many types of congenital malformation and the QRS axis may show extreme degrees of right axis deviation In the most extreme examples of right ventricular hypertrophy the QRS axis may come to point over the right shoulder giving prominent S waves in standard lead III which may erroneously be interpreted as left axis deviation The amplitude of the QRS complexes is as important as the QRS axis in evaluating ventricular hypertrophy QRS changes are always more specific than T wave abnormalities in indicating which ventricle is involved

Prolongation of the QRS duration beyond 0 12 sec is *uncommon* in congenital heart disease An rsR complex in precordial lead V1 and adjacent leads occurs frequently with right ventricular hypertrophy but the duration usually ranges from 0 06 to 0 11 sec This pattern has been termed "incomplete right bundle branch block" when the QRS duration is from 0 10 to 0 12 sec but the clinical significance in this situation is the same as with shorter QRS durations The Wolff Parkinson White conduction anomaly is not common in congenital heart disease except in Ebstein s disease

Prolonged P R intervals are particularly frequent with atrial septal defect and are found occasionally in other malformations Complete atrioventricular block is rare Although it is said to be common in ventricular septal defects its incidence in this anomaly has probably been overestimated Congenital complete heart block is a rare functional abnormality which may occur in the absence of other defects and is usually of no functional consequence

Supraventricular arrhythmias including atrial fibrillation and flutter atrial and nodal tachycardia and wandering of the pacemaker occur with many malformations particularly with atrial septal defect and with Ebstein s disease Ventricular arrhythmias are no more frequent than in acquired heart disease

Cardiac Catheterization Information obtained by catheterization of the right side of the heart has been essential to the development of knowledge in the field of congenital heart disease In many cases it gives an accurate indication of the lesions present and a quantitative estimate of their functional significance

In general three questions can be answered by cardiac catheterization

1 Are the pres ures and pressure gradients in the heart and vessels normal? The most important deviations from normal pressure relationships to be recognized are elevation of right ventricular or pulmonary artery pressure or an exaggerated pressure drop across a valve indicating stenosis

2 Is highly oxygenated blood admixed with systemic venous blood at any point? The finding of

cial since the blood viscosity increases as the *hematocrit rises* The resulting increase in heart work is undesirable but of even greater significance is the tendency to vascular thromboses Hemiplegia and other cerebrovascular accidents occur frequently in polycythemic congenital heart disease as a result of cerebral thrombosis Dehydration is particularly to be avoided in these patients since further reduction of plasma volume increases the predisposition to thromboses In some patients with cyanotic congenital heart disease polycythemia is accompanied by thrombocytopenia and low blood fibrinogen levels leading to impaired clot retraction Severe postoperative bleeding following the surgical repair of congenital cardiac defects can sometimes be attributed to this deficiency

Clubbing Clubbing of the fingers and less often of the toes is usually found in patients who have had cyanosis and polycythemia over a period of years The pathogenesis of such clubbing is unexplained but it may represent excessive growth of local tissue due to increased blood flow Clinically identical clubbing may occur with pulmonary disease

Impaired growth Impaired growth and development in children has been attributed to tissue hypoxemia in venous arterial shunts but it is open to question whether such a causal relationship exists Some children with congenital heart disease are unquestionably stunted in growth and development while others develop normally Underdevelopment may be associated with malnutrition from inadequate feeding or with the frequent respiratory and other infections to which these children are prone or it may represent a concomitant congenital defect

Squatting Many patients with tetralogy of Fallot and some with other lesions which obstruct blood flow to the lungs find that squatting with the knees drawn up to the chest is the most comfortable resting position They are uncomfortable and often show increasing cyanosis if made to stand quietly or if they are tilted passively on the fluoroscope table Their avoidance of postures in which the legs are dependent suggests that decreased venous return is the important factor in these phenomena but the mechanism is not well understood Squatting is also observed in many normal children and is an habitual resting position of adults in many parts of the world The posture is clinically significant only if it can be shown to give symptomatic relief after exertion

Paradoxical Embolism This condition in which emboli arising in the systemic veins travel through a defect and lodge in a peripheral artery is always possible with right to left shunts This is probably responsible in part for the increased incidence of brain abscess in these patients

Pulmonary Hypertension

In the normal adult the pulmonary circulation is a relatively low pressure system mean pulmonary artery pressures of 15 mm Hg or less being sufficient to maintain adequate flow through the lung at rest Moreover the normal pulmonary vascular bed can distend sufficiently to allow at least a threefold increase in cardiac output on exertion with no increase in pulmonary artery pressure When a large left to right shunt exists in congenital heart disease so that a larger volume of blood flows through the lung than flows out of the aorta per minute the resistance of the pulmonary vascular bed gradually increases and the right ventricle must create a higher than normal pressure head to push an adequate volume of blood per minute through the lungs This increased pulmonary vascular resistance is partly reversible but pathologic studies show that definite anatomic narrowing of the pulmonary arterioles plays at least some part in its genesis Whether the vascular changes seen under the microscope are themselves congenital in origin or whether they represent an acquired response to chronically increased pulmonary flow remains open to question

It seems clear that the absolute magnitude of pulmonary blood flow is not the only factor which influences the development of pulmonary hypertension Abnormally high pulmonary artery pressures are found more often with ventricular than with atrial septal defects and only occasionally with patent ductus arteriosus although pulmonary blood flow is often three or more times the systemic flow in all these abnormalities

The most important practical effects of pulmonary hypertension are (1) *right ventricular hypertrophy* with characteristic effects on the roentgenogram and electrocardiogram If the strain on the right ventricle is too severe or prolonged failure may supervene with the same increased venous pressure distention of the liver and peripheral edema seen in right ventricular failure from other lesions (2) *Enlargement of the pulmonary conus and pulmonary artery* which can be recognized by fluoroscopy or roentgenography and may give rise to hoarseness by compression of the left recurrent laryngeal nerve between the aorta and the pulmonary artery Precordial pain spontaneous or on effort is frequently a troublesome symptom in patients with a dilated pulmonary artery and pulmonary hypertension

The principal physical signs of pulmonary hypertension are accentuation of the pulmonic second sound splitting of the second sound in the pulmonic area and a systolic murmur attributable to turbulence as the blood enters the relatively large volume of the dilated pulmonary artery Such mur

blood which is more highly oxygenated than samples taken further upstream (a "step up" in oxygen saturation) may indicate a left to right shunt through a defect but interpretation of such measurements is sometimes difficult As a result of incomplete mixing of the incoming streams from the superior and inferior venae cavae and from the coronary sinus which normally has a very low oxygen content there is a normal variation between samples from the same chamber which is almost always less than 2 0 vol per cent Differences of this magnitude or greater usually indicate a left to right shunt and in some circumstances differences of 1 5 vol per cent may be significant This significance is increased if confirmed by multiple samples It follows that small left to right shunts causing lesser differences in oxygen content (which would include most shunts equal to less than 25 per cent of the systemic blood flow) may not be detected by the *usual technique of the right heart catheterization* Right heart catheterization will not ordinarily identify the site of a right to left shunt unless the indicator dilution technique described below is employed

3 Does the catheter follow an abnormal course or pass through an abnormal opening? Under the fluoroscope the catheter may sometimes pass through a congenital defect and thus provide *prima facie* evidence of an anomalous communication Such observations must however be interpreted cautiously for the fluoroscopic image of the catheter in a single plane does not always identify its anatomic location unequivocally Moreover it is not always possible to put the catheter where one wants it In occasional patients for example repeated attempts to advance the catheter into the pulmonary artery will fail even in the absence of pulmonary stenosis or other abnormality Failure to pass the catheter through a suspected defect is therefore of little significance

Catheterization studies are usually done with the patient at rest under conditions approaching as nearly as possible a steady basal state Alterations in this steady state during the procedure which may change the relative oxygen saturation of consecutive blood samples are to be avoided

In many cases a reliable diagnosis can be reached on the basis of history physical examination and roentgenographic and electrocardiographic studies and cardiac catheterization is not needed Unnecessary catheterization is obviously to be avoided although the risk is small A mortality of 0 07 per cent was reported in a total of 5 700 catheterizations in eight laboratories in the United States The risk in acyanotic patients with moderate symptoms is distinctly less than this figure and most of the fatalities occur in severely ill patients with pulmonary hypertension and cyanosis The procedure is particularly hazardous in patients with primary pulmonary hypertension

Catheterization of the right side of the heart is indicated when data so obtained are essential to the management of the patient as for example in deciding on surgical treatment One hesitates to use cardiac catheterization when the diagnosis is already reasonably clear from routine examination and surgery seems not indicated but if the diagnosis is uncertain it is better to secure the additional information provided by cardiac catheterization than to deprive a patient of possible surgical benefit With more malformations being added constantly to the list of those amenable to surgery it becomes increasingly important to identify the lesions in each case of congenital heart disease by catheterization or other appropriate methods

Left heart catheterization via a direct needle puncture through the bronchus or through the thoracic wall has been employed by a number of investigators with encouraging results The risk of this procedure cannot yet be evaluated but is almost certainly higher than that of intravenous right heart catheterization Its eventual place as a diagnostic measure remains to be determined

Pressure measurements by direct puncture during open thoracotomy are now routine in many surgical departments and can give valuable data concerning the lesion and the immediate results of surgery It should be emphasized however that measurements obtained in the presence of the relatively low cardiac output systemic pressure and pulmonary artery pressure of the anesthetized patient with an open chest may be radically different from those under more normal conditions

Indicator-dilution Curves The arterial time concentration curve after intravenous injection of a dye or radioactive indicator is often characteristically modified by the presence of a shunt With right to left shunts an early curve is superimposed on the normal one and in left to right shunts the repeated recirculation of dye through the shunt and the lungs gives a typically low prolonged curve (Fig 165 p 1302) This method is not so sensitive in detecting small shunts as is catheterization but it can be used to identify the *site* of a right to left shunt if successive injections are made through a catheter at different locations Injections distal to the site of the shunt produce normal arterial curves while injections proximal to the shunt give typical right-to-left shunt curves Dilution curves are therefore useful as a screening procedure and as an adjunct to cardiac catheterization

Phonocardiography Careful investigation of heart sounds and murmurs by phonocardiography has elucidated many auscultatory phenomena and provided a number of useful diagnostic facts In practice however recording of the phonocardio

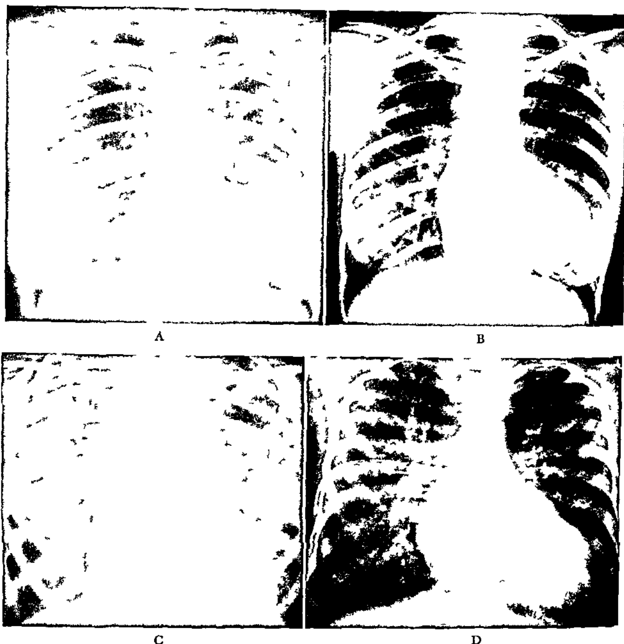


Fig 163 *A* Pure pulmonic stenosis with prominent poststenotic dilatation of the pulmonary artery in a 42 year old woman Pulmonary vascular markings in the peripheral lung fields are less prominent than in the normal person

B Tetralogy of Fallot in a girl 17 years of age Greatly increased transverse diameter with apex of the heart tipped up and relatively avascular lung fields (The three small radiopaque shadows at the upper margin of the film are artefacts)

C Anomalous drainage of all pulmonary veins into left innominate vein with typical figure 8 contour in a 4 year old boy

D Complete transposition of the great vessels in a 12 year old boy Note absence of normal pulmonary conus with narrowing of upper mediastinal shadow in this view prominent pulmonary vascular markings and ventricular enlargement

age ventricular septal defects and congenital stenosis of the mitral tricuspid and aortic valves These anomalies are enumerated in approximately the order of increasing operative risk which varies widely with the different lesions Closure of patent ductus arteriosus for example has been carried out in hundreds of patients since 1939 and the present operative mortality is about 2 per cent while open heart surgery on ventricular septal defect has been in use for a relatively short time and complete evaluation of the risks and results is not yet possible

The responsibility of deciding whether surgery is to be advised in an individual case should be shared by the internist and the surgeon The only rational basis for such a decision is accurate knowledge of the prognosis without operation in the case in question as compared with the risk and chances of benefit from surgery Under the best of conditions the factors which enter into this comparison are not as yet completely known

In general patients with physical signs of congenital heart disease but without symptoms clearly related to their heart disease should not undergo corrective surgery There are at least two exceptions to this generalization patent ductus arteriosus and coarctation of the aorta The chances of subacute bacterial endocarditis or other possibly fatal complications are so great with these two lesions that surgical correction should be considered in all affected patients under the age of thirty years even in the absence of symptoms

Patients with congenital malformations of the heart and symptoms which unmistakably limit their activity or give symptoms of increasing severity should be carefully studied as possible candidates for surgery

In estimating the severity of the burden imposed on the heart the patient s response to such ordinary activities as walking and climbing stairs is the best guide Dyspnea is a subjective phenomenon however and the patient s own estimate of his limitations may be misleading in either direction An objective test of myocardial competence in relation to ordinary activity is badly needed Measurement of cardiac output shunts and intracardiac pressure particularly under resting conditions do not sufficiently answer this need

In cases with severe and prolonged pulmonary hypertension the decision to operate is particularly difficult because some such patients have had no benefit or have died following technically successful correction of their defect Cases of patent ductus arteriosus with reversed flow (right to left) are the most striking examples of this dilemma Some such patients have been successfully treated surgically and no rule of thumb can be stated except to emphasize that patients who have developed sufficient pulmonary hypertension to reverse the direction of a shunt producing cyanosis even at rest are poor operative risks Prognosis for children with pulmonary hypertension following operation is better than that for adults in whom the inciting cause has existed for a longer period and the circulatory system is less adaptable

SPECIFIC MALFORMATIONS

Congenital heart disease includes such a variety of anatomic lesions and so many possible combinations of lesions that some system of classification is essential The classification most widely used at present based primarily on the presence or absence of cyanosis was introduced by Maude Abbott whose pioneer work in this field laid the foundation for much of modern knowledge

As useful as this system has been it has a number of disadvantages cyanosis is a subjective sign it occurs in a variety of lesions which have little else in common and it can be produced by at least three fundamentally different mechanisms (venous arterial shunt extreme peripheral desaturation inadequate pulmonary oxygenation)

A classification based on specific anatomic lesions rather than the clinical syndromes produced by combined lesions might be preferable The tetralogy of Fallot for example which is classed by Abbott as a cyanotic disease combines three specific lesions pulmonary stenosis overriding aorta and ventricular septal defect The clinical picture depends on the relative severity of these three malformations and usually includes decreased pulmonary blood flow and marked cyanosis If however the ventricular septal defect is large and the pulmonic stenosis and overriding of the aorta are mild in degree there may be increased pulmonary blood flow and no cyanosis

In the section which follows the Abbott classification has been modified and lesions are grouped according to their effect on blood flow as follows

I Malformations which permit shunting of blood
  A Initial shunt left to right
  B Initial shunt right to left
II Malformations which obstruct blood flow
III Malformations with no effect on blood flow

Class IA includes all lesions with an arteriovenous communication in which the normal pressure relationships after birth lead to a left to right shunt the potentially cyanotic group of Abbott The second subdivision *B* comprises Abbott s cyanotic group Class II includes most of the acyanotic" lesions of Abbott

Malformations with Potential Shunts

Initial Left to right Shunt *Atrial Septal Defect* This is the most common congenital lesion of the

gram is rarely necessary although it is helpful in occasional cases where the precise timing of an extra sound or the duration of a murmur is in question

COMPLICATIONS

In many types of congenital heart disease there appears to be a lowering of resistance to infections in general and to respiratory infections in particular A history of repeated attacks of bronchitis or pneumonia is common particularly in children and particularly with atrial septal defect In at least some cases malnutrition and underdevelopment may be ascribed to these recurrent illnesses Neither hypogammaglobulinemia nor deficient antibody formation seems to be concerned in this lowered resistance

Bacterial endocarditis acute or subacute is a common complication of congenital heart disease About 10 per cent of all cases of subacute bacterial endocarditis occur in congenital heart disease Patent ductus arteriosus ventricular septal defect coarctation of the aorta and bicuspid aortic valve are the lesions most likely to become infected while patients with atrial septal defect rarely develop this complication It may appear at any age but is commonest in young adults The symptoms signs and treatment of subacute bacterial endocarditis are the same with congenital heart disease as with other cardiac abnormalities Subacute bacterial endocarditis in patent ductus arteriosus is in itself an indication for surgical closure and this procedure alone will usually terminate the infection

Because of the susceptibility of many congenital cardiovascular malformations to bacterial endocarditis prophylactic antibiotic treatment should be *carried out during procedures which may produce* transient bacteremia such as dental extractions

Thromboses are common particularly in the cerebral circulation The high incidence in polycythemic patients and after dehydration suggests a relationship with blood viscosity Fluid intake should be carefully watched in such patients particularly in warm weather Cerebral thromboses may present with convulsions or sudden hemiplegia or they may be immediately fatal Treatment of the polycythemic patient is based on use of anticoagulant drugs venesection and hemodilution with intravenous isotonic fluids Continuous prophylaxis similar to that employed in rheumatic heart disease is not indicated however

Brain abscess is a serious complication of congenital heart disease which may appear any time after the first year or two of life It is more frequent in patients with right to left shunts since bacterial emboli by pass the lung filter and enter the brain Successful treatment depends largely on early diagnosis and the possibility of brain abscess should be considered promptly in any patient with congenital heart disease who develops unexplained fever headaches or other appropriate signs or symptoms

THERAPY

Medical Medical treatment of congenital heart disease consists mainly in the treatment of heart failure maintenance of myocardial compensation and prevention and treatment of complications

The congestive heart failure which occurs with congenital malformations of the heart does not differ essentially from that seen in other diseases of the heart and the principles of treatment are similar Digitalis is the keystone of therapy for establishing and maintaining cardiac compensation The choice of a digitalis preparation is dictated by the speed of action required and the personal prejudices of the individual physician There is no convincing evidence to show that the numerous digitalis preparations available differ in their clinical effects except in rapidity and duration of action

Many cases of congenital heart disease are instances of "high output failure" (see Chap 14) in the sense that at least one ventricle is required to pump more than its normal output per minute Digitalis is nevertheless just as effective in these cases as in the low output failure of most forms of acquired heart disease

In some situations myocardial failure eventually becomes intractable in spite of adequate digitalization and other therapy Acute left ventricular failure with pulmonary edema is treated with oxygen morphine tourniquets on the extremities elevation of the head of the bed and venesection (see Chap 226) In the polycythemic patient venesection *serves a double purpose by decreasing blood viscosity* as well as temporarily reducing total blood volume but it must nevertheless be used cautiously Right ventricular failure is more common than left in congenital heart disease and is usually a more chronic problem Salt restriction diuretics and the direct removal of fluid accumulations such as pleural effusions by thoracentesis are used to combat the tendency to retain water and salt

Digitalis toxicity is a frequent complication with consequences which can be as serious as those of the heart failure itself Frequent ventricular extrasystoles bigeminy and complete heart block are warning signs of digitalis overdosage which should be heeded

Surgical The congenital abnormalities which can be corrected or relieved by surgery at present comprise patent ductus arteriosus *pulmonary valvular* or infundibular stenosis (either isolated or in the tetralogy of Fallot) coarctation of the aorta atrial septal defect anomalous pulmonary venous drain

rection of the shunt may be reversed by complicating lesions such as an overriding aorta or by the gradual development of pulmonary hypertension Cases with extremely large defects or complete absence of the ventricular septum (single ventricle) are usually but not always cyanotic from birth

Symptoms in cases of isolated ventricular septal defect may appear in infancy or not at all depending on the size of the defect and the flow through it

A harsh systolic murmur of greatest intensity in the third and fourth interspace just left of the sternal edge is the classic sign of ventricular septal defect in the majority of cases it is accompanied by a thrill It usually extends throughout systole and is maximal in mid or late systole If pulmonary hypertension develops the systolic murmur decreases in intensity as the pulmonic second sound increases An apical diastolic murmur is present in most cases with large shunts

In the absence of symptoms the roentgenogram is often normal but may show increased pulmonary vascularity enlargement of both ventricles and often moderate left atrial enlargement The pulmonary artery and its branches are usually prominent and in patients with marked pulmonary hypertension may be greatly enlarged The electrocardiogram reflects whatever degree of combined right and left ventricular hypertrophy is present with normal axis or deviation to the right

Stenosis of the pulmonary valve or infundibulum may give a murmur similar to that of ventricular septal defect but it is usually loudest in the second or third interspace particularly with valvular stenosis The decreased pulmonary vascularity by x ray is the most important point in distinguishing these lesions from pure ventricular septal defect

The systolic murmur of atrial septal defect is occasionally quite loud and may even produce a thrill but it too is typically higher on the chest wall than in ventricular septal defect Moreover with atrial septal defect left ventricular hypertrophy does not occur unless mitral incompetence is also present In ventricular septal defect with marked pulmonary hypertension right ventricle enlargement predominates and differentiation from atrial septal defect by clinical means may be impossible Confusion may also arise in patients with mitral insufficiency where the murmur is more medial than usual but such a lesion produces left ventricular enlargement without right ventricular enlargement unless other valve lesions are present

Ventricular Septal Defect in Combination with Other Lesions Approximately 9 of every 10 patients with an interventricular septal defect also have other cardiac malformations of which the most common are pulmonary stenosis and overriding of the aorta Aortic incompetence due to an anomalous aortic cusp is an occasional complicating lesion of considerable importance because the murmurs and wide pulse pressure may lead to an erroneous diagnosis of patent ductus arteriosus

Eisenmenger's complex is the name of a condition in which there is a defect of the membranous ventricular septum with the relatively late appearance of cyanosis usually in adolescence Overriding of the aorta is regarded by some as an essential part of this syndrome but mild degrees of overriding are difficult to recognize even at autopsy and the diagnosis is based primarily on the clinical course Most patients designated as having Eisenmenger's complex probably have simple ventricular defects and gradually develop pulmonary hypertension with reversal of the shunt

Patent Ductus Arteriosus The ductus arteriosus which is an essential communication between the pulmonary artery and aorta during fetal development normally closes before the age of two years It may atrophy and disappear completely or persist as a solid cord.

Persistent patency of the ductus arteriosus beyond this age is a common abnormality representing approximately 10 per cent of all congenital malformations seen clinically The lumen varies from 5 to 10 mm in most patients With the normally existing pressure gradients there is a left to-right shunt from the aorta to the pulmonary artery but this varies greatly in magnitude in different patients and is often well tolerated The majority of patients with this anomaly are asymptomatic and are unaware of its existence until it is discovered on routine physical examination

The open ductus provides a low resistance pathway from the aorta during diastole as well as systole and a lowering of the arterial diastolic pressure results The arterial pulse pressure is thereby widened just as in aortic regurgitation

The left ventricle bears the burden of the shunt showing hypertrophy and enlargement in cases where the shunt is large enough to cause symptoms As in other left to right shunts continued high pulmonary blood flow is sometimes followed by the development of pulmonary hypertension This tends to decrease the left to right shunt and if the pulmonary artery pressure reaches systemic levels the flow through the ductus will be reversed with cyanosis of the toes and the area of the body nourished by branches of the aorta distal to the ductus In such cases cyanosis may appear at first only with exertion but if the patient survives the right-to-left shunt becomes permanent even at rest

When the ductus enters the aorta distal to the great vessels of the aortic arch as is customary a venous arterial shunt through it gives rise to the almost pathognomonic finding of cyanosis of the

heart The defects may be single or multiple and vary in size from an open foramen ovale to complete absence of the interatrial septum (cor triloculare biventriculare) Patency of the foramen ovale with an unsealed valve which persists in 5 to 20 per cent of the adult population becomes significant only if the pressure in the right atrium rises to a level higher than that in the left atrium causing a right to left shunt

Atrial septal defects may be divided into two general types *persistent ostium secundum* (cephalad or midseptal in location) and *persistent ostium primum* (caudad with one margin of the opening made up by the tissue between the atrioventricular valves) This distinction has a practical value for the surgeon since the persistent ostium primum is technically much more difficult to repair It also serves a clinical purpose in that the ostium primum type of defect is often accompanied by persistence of the atrioventricular cleft in the mitral and tricuspid leaflets which may cause clinically recognizable insufficiency of one valve or of both

In the normal person mean pressure is usually several millimeters of mercury higher in the left atrium than in the right When an atrial septal defect is present there is a predominant left to right shunt through it although streamlining of flow may produce a small right to left shunt as well If right ventricular resistance to filling increases as with the development of pulmonary hypertension or right ventricular failure the shunt may become predominantly right to left

The clinical effects of an atrial septal defect depend primarily on the size of the defect and the volume of the shunt through it An undetermined proportion of cases remain asymptomatic throughout adult life

In patients who develop symptoms the earliest complaints are exertional dyspnea and fatigue The gracile habitus shown by some children with this defect is relatively rare and the average patient shows normal growth and development unless there is an unusually large shunt Cyanosis and symptoms from pulmonary hypertension are not encountered until late in the disease if at all

A systolic murmur in the pulmonic area is the most prominent physical finding Its origin is not certain but most probably it arises from the increased flow through a normal pulmonic valve into a dilated pulmonary artery Flow through the defect itself apparently does not contribute to this murmur since it is often unchanged after surgical closure of the defect The second pulmonic sound is often widely split

Fluoroscopy shows a greatly enlarged pulmonary conus and pulmonary arteries increased pulmonary vascularity a "hilar dance" and enlargement of the right atrium and right ventricle The electrocardiogram shows signs of right ventricular hypertrophy in almost all symptomatic cases It has frequently been stated that the electrocardiogram in this malformation usually shows right bundle branch block but it is more accurate to say that an rsR pattern is often found in VI and other right precordial leads usually with a QRS duration less than 0 12 sec This rsR pattern in itself is probably an indication of right ventricular hypertrophy Paroxysmal atrial tachycardia atrial fibrillation and prolongation of the P R interval are all common

The above findings apply to the persistent ostium secundum type of defect and to those ostium primum defects in which the mitral valve functions normally In some cases a persistent ostium primum is complicated by severe regurgitation through one or both atrioventricular valves usually the mitral In these cases symptoms almost always appear in childhood and an apical systolic murmur plus radiologic and electrocardiographic signs of *left* ventricular hypertrophy as well as right reveal the mitral lesions Signs of free tricuspid insufficiency also favor the diagnosis of persistent ostium primum

Cardiac catheterization will usually establish the diagnosis subject to the general limitations of this procedure discussed above The differential diagnosis between atrial septal defect and anomalous pulmonary veins draining into the right atrium is often impossible

The majority of atrial septal defects are not complicated by other congenital lesions except for the tricuspid and mitral valve deformities mentioned The combination of atrial septal defect and mitral stenosis (Lutembacher's syndrome) appears to be much less common than previously supposed Modern diagnostic methods and surgical exploration have shown that an apical diastolic murmur is often present in cases of atrial septal defect when the mitral valve is entirely normal and the diagnosis of Lutembacher's syndrome should therefore be made with considerable caution

Ventricular Septal Defect This is the second most frequent congenital anomaly of the heart More than 90 per cent are defects of the membranous portion of the septum the remainder being in the muscular portion and usually unaccompanied by other cardiac malformations They vary in size from very small ventricular defects which produce a loud systolic murmur but no symptoms throughout adult life (*maladie de Roger*) to complete absence of the interventricular septum (*single ventricle cor triloculare biatriatum*)

In cases of *uncomplicated* ventricular septal defect the normally higher pressure in the left ventricle produces a left to right shunt but the di

anomalous drainage the pulmonic and systemic venous blood are mixed in the right atrium and pulmonary arterial and aortic blood are equally unsaturated Pulmonary artery pressure is usually normal or slightly elevated in occasional patients it may rise to a mean of 70 mm Hg or more

Cardiac catheterization can demonstrate the left to right shunt and step-up in oxygen saturation in the right atrial blood but cannot distinguish between anomalous pulmonary venous drainage into the right atrium and atrial septal defect unless the catheter actually passes out one of the pulmonary veins from the vena cava or the right atrium Even this finding is often equivocal since it is difficult to be sure that the catheter has not passed into normally draining pulmonary veins by way of an atrial septal defect The situation is further complicated by the frequent association of the two anomalies Angiocardiography can be helpful in demonstrating anomalous pulmonary veins draining into the venae cavae or coronary sinus but it does not rule out concomitant atrial septal defect In many cases therefore differential diagnosis of these two malformations can be made only at thoracotomy

When the anomalous veins drain only one lung a specialized application of the dye dilution method may establish the diagnosis Injection of dye or other indicator into first one and then the other main branch of the pulmonary artery will give a normal dilution curve in the systemic arteries after injection into the normally drained lung and a curve typical of a left to right shunt after injection into the anomalously drained pulmonary bed

As has been indicated many patients with partial anomalous pulmonary venous drainage are without symptoms and therapy is not needed In others however and particularly in the total anomalies signs of right heart failure develop because of a large shunt or pulmonary hypertension or both In these patients surgical intervention should be considered although with total anomalies and with marked pulmonary hypertension the risk of operation is high

Initial Right to-left Flow These are the cases of cyanotic congenital heart disease" in which the malformed structure of the heart and great vessels exposes the right ventricle to the systemic circulation from birth and the fetal predominance of the right ventricle therefore persists

The partitioning of the embryonic truncus arteriosus into pulmonic and aortic channels is a key stage in the development of the heart and anomalies in this process underlie a number of clinical malformations including complete transposition of the great vessels Fallot s tetralogy the Eisenmenger complex and some defects of the membranous portion of the interventricular septum An understanding of this episode in the development of the human fetus is essential to a logical appreciation of these lesions and the excellent reviews of Harris and Farber and Patten are recommended

Deviations in the location of the partitioning septum can produce great variations in the relative size of the aorta and pulmonary artery as in the very large pulmonary artery in Eisenmenger s complex Failure of the normal twisting of the truncus may leave the aorta in direct communication with the right ventricle only and the pulmonary artery with the left ventricle as in complete transposition The almost unlimited permutations and combinations of such developmental errors can lead to the most complex malformations

The caudad end of the truncus septum is contiguous with the membranous portion of the interventricular septum and with the edge of the interatrial septum which closes the ostium primum Any abnormality of development in this relatively small area in the fetus—an area perhaps 1 mm in diameter in the eight week old embryo—can give rise to such apparently diverse anomalies as transposed great vessels defects of the interatrial and interventricular septum and anomalies of the atrioventricular valves

Transposition of the Great Vessels In this malformation the failure of normal torsion of the primitive truncus leaves the aortic root opening into the right ventricle and the pulmonary artery into the left This separation of the pulmonic and systemic circulation into two independent circuits is obviously incompatible with life unless some additional anomaly provides a communication between them Complete transposition of aorta and pulmonary artery is therefore not seen clinically except in combination with other anomalies such as patent foramen ovale atrial septal defect ventricular septal defect or patent ductus arteriosus The bronchial arteries provide an additional shunt pathway in many cases The larger the communication the better the patient s chances for survival

In patients with these conditions the paths of blood flow are not yet fully understood but they involve mixed shunts which may reverse their direction from systole to diastole There is usually marked lowering of peripheral arterial saturation with cyanosis and polycythemia

Signs and symptoms including cyanosis are present from birth and rapid cardiac enlargement during the first year of life is the rule The malformation is occasionally seen in older children but the majority of the infants affected die during the first year unless compensating anomalies coexist

A precordial bulge is frequently present owing to the early cardiac enlargement and the precordial pulsation is indicative of dominant right ventricular enlargement The second pulmonic sound is

lower extremities with normally pink upper extremities Once this stage has been reached the prognosis is poor and survival for more than a year or two is exceptional

The classic murmur of patency of the ductus extends through systole and diastole as does the flow of blood through the ductus The murmur reaches its maximal intensity about the end of systole and overrides the second sound which may be completely obliterated It may begin with the first sound or in early systole and may extend throughout diastole or die away in late diastole The second left interspace at the sternal border is most often the area of maximal intensity The systolic element may be heard over most of the precordium and above the clavicles while the diastolic is sometimes less widely transmitted As in other left to right shunts a separate apical diastolic murmur from relative mitral stenosis is sometimes heard

Pulmonary hypertension modifies the typical murmur just as it modifies the size and direction of the shunt With roughly equal pressures in aorta and pulmonary artery and little or no shunt the murmur may disappear entirely while under other circumstances either the diastolic or the systolic component may be absent

Fluoroscopy may show a prominent pulmonary conus slight right and left ventricular enlargement slight increase in pulmonary vascularity or no abnormality at all The electrocardiogram may show moderate left or combined ventricular hypertrophy but is more often within normal limits

Patent ductus arteriosus can occur in combination with many other malformations In some instances such as complete pulmonary atresia a patent ductus performs an essential function by carrying blood to the lungs

Differential diagnosis is relatively easy in the average patient with a typical murmur and no cyanosis Although many other lesions produce both systolic and diastolic murmurs the two murmurs are usually separate and do not continue through the second sound Defects of the septum between the ascending aorta and pulmonary artery are an exception to this rule which is not surprising since this anomaly is physiologically identical with patent ductus except for the slightly more proximal site of the communication Cardiac catheterization may be of help in differentiating between patent ductus arteriosus and such aortic septal defects if the catheter passes through the defect Retrograde aortography may establish the diagnosis

Anomalous Pulmonary Venous Drainage This is a relatively uncommon malformation although its incidence is not accurately known A review of the literature in 1950 by Smith revealed only 133 published cases but increasing numbers of cases are being discovered by catheterization and surgery The most frequent sites of drainage are the superior vena cava the right atrium the left innominate vein and the coronary sinus The effects of this malformation depend on whether all or only part of the blood from the lungs is returned to the right heart Total anomalous pulmonary venous drainage requires an associated patent foramen ovale or atrial septal defect to allow blood to reach the systemic circulation while partial anomalous drainage in which some pulmonary veins enter the right side of the heart while others enter the left atrium normally may occur without other complicating lesions

Partial anomalies are often well tolerated and may be entirely asymptomatic while total anomalous drainage is a much more severe handicap less than a fifth of patients with the latter condition survive beyond infancy

In both situations there is a left to right shunt and therefore increased pulmonary blood flow but the size of the shunt varies greatly In patients with total anomalous pulmonary venous drainage there may be a history of cyanosis at birth and infancy and mild degrees of cyanosis at rest or on exertion and even clubbing in later life

Physical signs may be lacking in cases of partial anomalous pulmonary venous drainage but in the total anomalies there is almost always a grade 2 to 4 systolic murmur often with a thrill in the second to fourth intercostal space at the left sternal border This is probably related to an associated atrial septal defect and the accompanying dilatation of the pulmonary artery A softer continuous murmur is often heard in the aortic area probably a true venous hum from increased flow through the anomalous veins

Roentgenograms are characteristic in three specific patterns of anomalous pulmonary venous drainage (1) a common right pulmonary vein draining into the inferior vena cava which adds a smooth semicircular shadow to the right heart border (2) total pulmonary venous drainage into a persistent left superior vena cava giving a "figure 8 or "snowman contour to the whole cardiovascular silhouette (Fig 163C) (3) total pulmonary venous drainage into the coronary sinus in which the greatly dilated coronary sinus and anomalous veins displace the esophagus posteriorly simulating left atrial enlargement The electrocardiographic findings are normal in most asymptomatic patients and show signs of right ventricular hypertrophy as symptoms become predominant

Hemodynamically the systemic flow is normal or slightly lowered while the left to right shunt gives an increased pulmonary flow varying from one and one half to five or more times the systemic flow Peripheral arterial oxygen saturation may be normal with partial anomalies but with totally

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The caudad end of the truncus septum is contiguous with the membranous portion of the interventricular septum and with the edge of the interatrial septum which closes the ostium primum Any abnormality of development in this relatively small area in the fetus—an area perhaps 1 mm in diameter in the eight week-old embryo—can give rise to such apparently diverse anomalies as transposed great vessels defects of the interatrial and interventricular septum and anomalies of the atrioventricular valves

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In patients with these conditions the paths of blood flow are not yet fully understood but they involve mixed shunts which may reverse their direction from systole to diastole There is usually marked lowering of peripheral arterial saturation with cyanosis and polycythemia

Signs and symptoms including cyanosis are present from birth and rapid cardiac enlargement during the first year of life is the rule The malformation is occasionally seen in older children but the majority of the infants affected die during the first year unless compensating anomalies coexist

A precordial bulge is frequently present owing to the early cardiac enlargement and the precordial pulsation is indicative of dominant right ventricular enlargement The second pulmonic sound is

greatly accentuated and not split Systolic murmurs and thrills are usually found but are related to the associated defects rather than to the transposition itself Some patients with a patent foramen ovale or patent ductus arteriosus have only faint systolic murmurs or none at all

The radiologic picture is often characteristic (see Fig 163D)

When the ascending aorta lies directly ventral to the pulmonary trunk their shadows are superimposed giving an unusually narrow upper mediastinal shadow and an absence of the usual pulmonary conus The pulmonary arteries and smaller vessels are large and pulsate vigorously Both ventricles and often both atria are enlarged Right axis deviation and marked right ventricular hypertrophy are found in the electrocardiogram

The diagnosis can usually be made from the history and roentgenologic features On cardiac catheterization the catheter may enter the aorta and the characteristically anterior origin of the aorta may be identified in the lateral view

A variant of this anomaly is complete transposition of the aorta with only partial transposition of the pulmonary artery so that the pulmonary artery overrides the right ventricle and a high ventricular septal defect (*Taussig Bing complex*) Although this malformation differs developmentally from the Eisenmenger complex the clinical pictures are similar The single distinguishing feature is the appearance of cyanosis at birth in the Taussig Bing complex as contrasted with its later appearance in the Eisenmenger complex

Persistent Truncus Arteriosus This is a rare anomaly in which blood flows from both ventricles into a single common trunk overriding a high ventricular ventral defect Blood reaches the lungs through pulmonary arteries branching from this trunk There may be a right or left aortic arch

Cyanosis is present but its degree depends on the relative proportions of pulmonary blood flow and venous arterial shunt Pulmonary blood flow exceeds normal values if there is free communication from the truncus to the lungs and no pulmonary vascular changes occur This increased pulmonary blood flow mixing with the systemic venous return often results in an almost normal oxygen content of arterial blood in spite of a large right to left shunt If two pulmonary arteries branch from the main trunk normal pulmonary blood flow obtains and cyanosis is minimal If only one small pulmonary artery leaves the truncus total pulmonary blood flow will be reduced If none of the pulmonary artery remnants communicates with the truncus directly the bronchial arteries may provide the only pathway for blood flow to the lungs Pulmonary blood flow is low and cyanosis is intense There is some confusion in the terminology applied to this condition which is sometimes termed "pseudo truncus Anatomically it more closely resembles tetralogy of Fallot than the usual truncus arteriosus

In infants the roentgenogram may be diagnostic with a sharp right angle between the shelflike upper surface of the right ventricle and the aorta in the left anterior oblique view With increasing age this disappears and the great right ventricular enlargement and absent pulmonary conus give a picture similar to that in Fallot s tetralogy

In *tetralogy of Fallot* the essential features are actually three in number pulmonary stenosis high ventricular septal defect and dextroposition of the aorta so that it overrides the defect The right ventricular hypertrophy which completes the tetralogy is a consequence of the abnormal hemodynamics induced by these three lesions

Fallot s tetralogy is the most common combination of lesions which leads to early cyanosis yet often allows survival into adult life The stenotic obstruction is usually in the infundibulum or right ventricular outflow tract, but may be in the valve itself or at both sites Dilatation of the pulmonary artery beyond the stenosis is usually not striking In some instances there is complete atresia of the pulmonary artery and blood reaches the lung through other channels a condition sometimes confusingly referred to as "pseudo truncus arteriosus" A large right to-left shunt is present with cyanosis appearing either at birth or within the first two years Clubbing and polycythemia follow at an early date The pulmonic stenosis produces a characteristic murmur described below and decreased pulmonary vascularity The electrocardiogram shows right ventricular hypertrophy The size of the heart radiologically is usually normal but the normal leftward convexity of the pulmonary conus is missing In some cases the apex of the heart is somewhat tipped up" in the anteroposterior view (see Fig 163B) A right aortic arch occurs in about 25 per cent of patients and can be seen to indent the barium filled esophagus to the *left* in the anteroposterior view and *posteriorly* in the left anterior oblique view

In rare cases usually in infants there may be only moderate pulmonic stenosis and a left to-right shunt Such cases of "atypical" or "acyanotic" tetralogy of Fallot have normal or increased pulmonary vascularity and diagnosis is often difficult

In the typical case the diagnosis can usually be made clinically These patients are more cyanotic than the usual case of uncomplicated pulmonic stenosis and do not have the greatly enlarged heart of complete transposition of the great vessels or the enlarged pulsating pulmonary artery of Eisenmenger s complex

Although many patients with tetralogy of Fallot reach adult life their exercise tolerance is invariably

limited and very few survive beyond the age of thirty years The Blalock Taussig operation provides an increased blood flow to the lungs through an artificial ductus relieving the cyanosis and clubbing and greatly increasing ability to exercise

Anomalous Origin of Coronary Arteries This is a rare malformation in which one coronary artery usually the left arises from the pulmonary artery A few cases with both coronary arteries arising from the pulmonary artery have been reported Although this must be classed as a right to left shunt strictly speaking its direct effects are limited to the heart muscle itself The combination of low coronary perfusion pressure and low oxygen tension seriously impairs myocardial function Severe congestive heart failure and cardiac enlargement appear in the first few months of life Pulmonary and peripheral edema may both develop The electrocardiogram shows ST and T wave abnormalities strikingly similar to those seen in adults with acute myocardial infarction (see Fig 164) Murmurs are usually absent Differentiation from other rare causes of early cardiac enlargement without cyanosis or murmurs discussed later in this chapter is based principally on the characteristic electrocardiographic changes

Malformations Which Obstruct Blood Flow

Pulmonary Stenosis This may involve either the pulmonic valve or the pulmonary infundibulum Since it is often associated with other anomalies the terms *pure* or *isolated* pulmonic stenosis are often used to indicate the absence of complicating lesions Cases of valvular stenosis with normal ventricular septum are much more common than previously thought and may constitute as much as 10 per cent of all patients with congenital heart disease The degree of stenosis varies from slight narrowing to a domelike membrane with only a pinhole opening

The principal effects of this lesion are reduction of the pulmonary blood flow and right ventricular hypertension and hypertrophy When the right ventricle can no longer maintain the high pressure needed to propel blood through the lungs congestive failure supervenes with the increased peripheral venous pressure hepatic distention and peripheral edema characteristic of right ventricular failure No shunt is present in uncomplicated cases but if the foramen ovale is unsealed and the pressure in the right atrium increases sufficiently a right to left shunt may result

Patients with mild degrees of pulmonary stenosis may have no symptoms and have an excellent prognosis In more severe cases the age of onset of symptoms—primarily exertional dyspnea or syncope—and of cyanosis varies widely but in the average case is during adolescence With increasing age the proportion of patients with cyanosis increases Cyanosis is not invariably indicative of right to-left shunt in this anomaly for an appreciable number will show clinical cyanosis presumably of peripheral origin even while the arterial saturation is normal Exertional dyspnea usually precedes the appearance of cyanosis and for some time is more striking than the cyanosis Once cyanosis has appeared the course is usually progressively downhill but there are striking exceptions to this rule and occasional patients continue to exhibit cyanosis on exertion for 20 years or more with little change Clubbing is present in proportion to the severity and duration of cyanosis

The most important physical signs of pulmonic stenosis are a systolic murmur with maximal intensity (usually at least grade 4) in the pulmonic area and a diminished or absent second pulmonic sound Phonocardiograms reveal a splitting of the second sound but only the first (or aortic) component may be audible With infundibular stenosis the site of greatest intensity is somewhat lower in the third to fourth interspace at the left sternal border The murmur terminates before the second pulmonic sound Diastolic murmurs are not usually present a point which is helpful in differentiating this lesion from ventricular septal defect Signs of right ventricular failure including enlargement and sometimes pulsation of the liver develop in the most severe instances

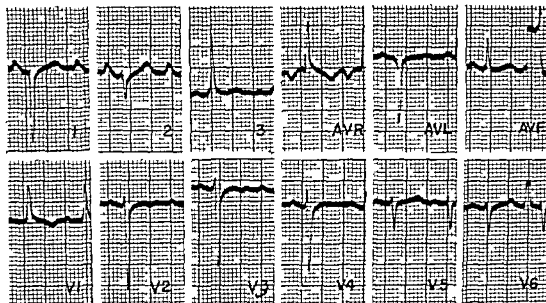
Radiographic study shows a prominence or actual enlargement of the pulmonary artery and its main branches the so-called "poststenotic dilatation" (see Fig 163A) with valvular stenosis but usually not with infundibular stenosis The pulmonary arteries do not pulsate actively as a rule but with mild stenosis slight pulsation may occur The vascularity of the lungs is diminished giving a relatively clear appearance to the peripheral lung fields In mild cases the ventricles are of normal size while in severe cases the right ventricle may be enormously enlarged The right atrium usually enlarges along with the right ventricle

Electrocardiographic signs of right ventricular hypertrophy are usually in proportion to the severity of symptoms and moreover it is with this lesion that the most striking right axis shift and increase in the amplitude of the R wave over the right precordium (2 0 mv and more) are seen Right atrial enlargement is reflected by increase in the P wave amplitude most prominently in standard lead 2

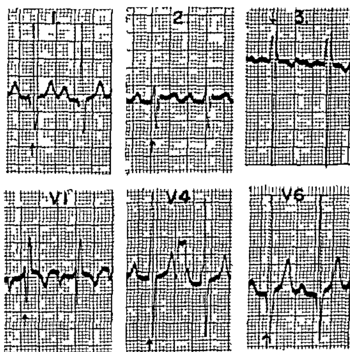
The most important hemodynamic finding is an increase in right ventricular pressure and the demonstration of a large pressure gradient across the site of the stenosis Right ventricular systolic pressure in symptomatic patients is usually between 60 and 180 mm Hg but one patient with a pressure as high as 270 mm Hg has been reported The pres

sure drop across the stenosis is often 100 mm Hg or more The systemic flow is usually slightly below normal but not so much below as one would expect from the severity of symptoms One critical handicap in patients with this condition is their limited ability to increase pulmonary flow on exercise even with considerable increase in right ventricular pressure In extreme instances exertion may lead to syncope

Cases showing early cyanosis must be differentiated from tetralogy of Fallot and those with late onset of cyanosis from Eisenmenger's complex A



A



B

Fig 164 A Electrocardiogram from a 9 year old girl with pure pulmonic stenosis The right axis deviation in the limb leads tall R wave in lead V1 and reversal of the normal precordial transition indicate marked right ventricular hypertrophy Note that precordial leads were recorded at half normal sensitivity

B Electrocardiogram from a 5 year old boy with an atrial septal defect ("persistent ostium primum")

prominent pulmonary artery and marked dyspnea with relatively little cyanosis help to rule out tetralogy of Fallot, while clear lung fields and absence of pulmonary artery pulsation are not found in Eisenmenger's complex. Cardiac catheterization can furnish direct evidence of the stenosis and the degree of right ventricular hypertension. Accurate diagnosis is of particular importance because the Blalock-Taussig operation does not benefit patients with isolated pulmonic stenosis, the increased left to right shunt apparently being the last straw for an already overburdened right ventricle, which rapidly fails. The Brock procedure of pulmonary valvotomy is the treatment of choice.

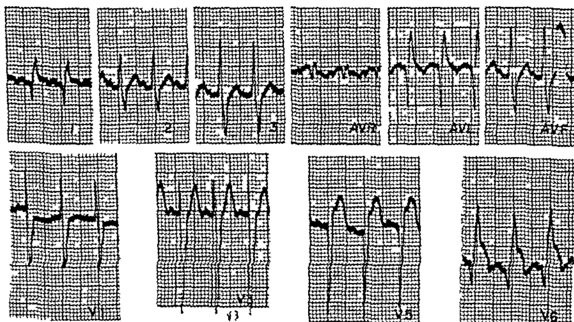
Other malformations may be found in combination with pulmonic stenosis, including anomalous pulmonary veins, atrial or ventricular septal defects, and patent ductus arteriosus.

The prognosis is good in uncomplicated cases without cyanosis, cardiac enlargement, or electrocardiographic signs of right ventricular hypertrophy. When any of these findings is present with severe or increasing symptoms, surgical relief of the stenosis should be considered. In borderline cases the right ventricular systolic pressure is a useful guide to prognosis, and systolic pressures greater than 100 mm Hg are usually an indication for operation.

Coarctation of the Aorta. This obstructive lesion results from an abnormal obliteration of the aorta during regression of the multiple aortic arch system of the embryo. The common classifications are based largely upon the age at death (infantile and adult) and on the site of coarctation in relation to the ductus arteriosus. The infantile or preductal type occurs in the aortic arch or just proximal to the ductus arteriosus, which is usually patent. Commonly there are other intracardiac defects which account for death at an early age. In most instances blood from the pulmonary artery supplies the lower half of the body (through the ductus) and the toes are cyanotic often in contrast to the fingers.

Postductal or adult coarctation is usually located immediately distal to the left subclavian artery, and a narrowed or obliterated ductus enters the segment proximal to the coarctation. Bicuspid aortic valve is present in 25 to 40 per cent of cases, but otherwise the heart is normal. In rare instances coarctation may be in the midthoracic aorta, at the diaphragm, or even in the abdomen.

The presenting signs are hypertension in the arms



C

and cleft mitral leaflet producing mitral regurgitation. Combined right and left ventricular hypertrophy are indicated by the left axis deviation, tall R V1, and tall R V6. A double R wave is present in lead V1, with QRS duration of 0.09 sec, and the P-R interval is prolonged. (Arrows indicate the peak of R 1 and synchronous points in other leads.)

C. Electrocardiogram from a male child aged 4 months with anomalous origin of the left coronary artery from the pulmonary artery. The prominent Q wave and S-T elevation in leads 1, V5, and V6 are characteristic of anterior myocardial infarction.

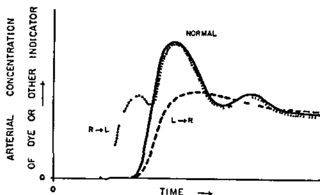


FIG 165 Schematic representation of arterial indicator dilution curve after intravenous injection of Evans blue dye or other indicator in normal persons (——) patients with right to left shunts ( ) and left to right shunts ( )

proximal to the obstruction and hypotension or absent pulses in the legs distal to it by these signs the diagnosis is made In the preductal type the associated intracardiac defects are prominent and incapacitating and the clinical picture is largely determined by these defects Patients with a postductal coarctation characteristically are troubled either early in life or a number of years later A few infants develop cardiac failure because of the load placed upon the left ventricle but most patients with coarctation of the aorta weather early childhood without symptoms or diagnosis Heart failure in an infant suggests some other lesion notably endocardial fibroelastosis for most infants with coarctation develop collateral circulation and hypertension is not striking until late childhood or adulthood Complaints rarely arise from diminished flow to the legs

In addition to the pathognomic pulse and pressure gradients there are striking pulsations in the neck and supraclavicular areas Systolic murmurs may be heard posteriorly from the coarctation or anteriorly from an abnormal aortic valve and diastolic murmurs may arise from collateral circulation Enlarged collateral vessels may be felt in the interscapular and subscapular areas

Notching of the ribs is the most characteristic radiologic observation caused by dilatation and tortuosity of intercostal arteries carrying the collateral flow A three sign may be produced in roentgenograms of the left upper mediastinum by the enlarged left subclavian artery the constriction at the coarctation and poststenotic dilatation distal to it

The electrocardiogram may be normal or may show left axis deviation and signs of left ventricular hypertrophy

In addition to cardiac failure most of these patients suffer from cerebral accidents rupture of the aorta or other complications of hypertension On occasion coarctation is associated with long life but 51 per cent of patients with this condition die before the fortieth year

The pathologic physiology has been of considerable interest because hypertension in this disease is associated with a discrete lesion which can be surgically corrected In addition to increased resistance from the constriction and the collateral vessels a renal mechanism activated by the lowered renal blood flow and pressure seems to contribute to this hypertension

Surgical correction is indicated in most children and also in adults in whom hypertension is great or symptoms related to it are present The segment can be excised and end to end suture performed in most instances but in some cases a graft may be required to bridge the gap or to obtain a satisfactory lumen

Stenosis or Atresia of Other Valves Congenital stenosis of the mitral tricuspid or aortic valves is uncommon Except for the relatively early appearance of signs and symptoms as compared with their counterparts in rheumatic heart disease the effects are similar *Tricuspid atresia* is usually associated with an underdeveloped or absent right ventricle atrial septal defect and atretic pulmonary artery Blood flows from the right into the left atrium and left ventricle and reaches the lungs through a patent ductus arteriosus The right ventricular cavity is absent or filled with blood clot or it communicates with the left ventricle through a ventricular septal defect but does not function Left axis deviation in the electrocardiogram results and this finding in a cyanotic patient is virtually pathognomonic of tricuspid atresia

Aortic atresia extremely rare is associated with a hypoplastic nonfunctioning left ventricle and frequently with *mitral atresia* as well Blood flows from left atrium to right atrium to the lungs and reaches the systemic circuit only through a patent ductus Survival for more than a few weeks is rare

Malformations without Direct Effect on Blood Flow

Dextrocardia and Situs Inversus Dextrocardia may occur as an exact mirror image reversal of the heart within the thorax (*true dextrocardia*) or as abnormal rotation of the heart with twisting of the great vessels (*dextroposition* or *dextrorotation*) of the heart Situs inversus or reversal of all the viscera may accompany any form of dextrocardia or it may occur with normal heart position Neither dextrocardia nor situs inversus is of any functional significance in itself but additional cardiac malformations are common and may be severe Mirror

image dextrocardia produces an almost pathognomonic electrocardiogram in the limb leads

Ebstein s Disease The rare anomaly of the tricuspid valve which bears this eponym consists of a congenital downward displacement of the valve into the right ventricle with anomalous insertion of one or more valve leaflets The malformation sometimes produces surprisingly little functional disturbance while in other cases incompetence of the tricuspid valve and impaired function of the right ventricle produce prominent signs at an early age Sudden death has often been reported

Although patients with Ebstein s disease are not cyanotic in infancy they may eventually develop right to left shunts through a patent foramen ovale The right atrium and right ventricle are then greatly enlarged and the pulmonary vascularity may be decreased The electrocardiogram shows tall P waves but no signs of ventricular hypertrophy Complete right bundle branch block and paroxysmal tachycardia are common There is often an apical systolic murmur which is attributed to incompetence of the dislocated tricuspid valve

Anomalies of the Aortic Arch The multiple bilateral aortic arches of the embryo provide a background for a great variety of anomalies One of the commonest is a *right aortic arch* in which the ascending aorta arches toward the right instead of the left The aorta may then continue to lie on the right in its descent or may cross over to descend in the normal position just left of the midline In either case the anomaly is of no functional significance A right aortic arch may be recognized by its indentation of the barium filled esophagus since it impinges on the *right* side of the esophagus in the anteroposterior view and displaces the esophagus backward in the left anterior oblique view

In some cases both right and left aortic arches persist forming a vascular ring Such a ring which may also result from anomalies of the subclavian or other arteries usually has no effect on cardiac function but it may produce symptoms by compression of the esophagus or trachea

Anomalies of the Great Veins Many variations in the structure of the superior and inferior venae cavae and their major branches are possible A persistent left superior vena cava for example is a fairly common anomaly Anomalous venae cavae may drain normally into the right atrium and be of no functional significance or they may drain into the left atrium producing major venous arterial shunts The course of such anomalies can usually be clearly outlined by angiocardiography

Congenital Cardiac Hypertrophy On rare occasions cardiac dilatation and hypertrophy with congestive heart failure develop during the first few months of life in the absence of cyanosis thrills or murmurs In a few of these cases no clear etiologic factors can be discovered even on pathologic examination and they are accurately termed *idiopathic congenital cardiac hypertrophy*

The same clinical picture may be produced by a variety of causes including endocardial fibroelastosis von Gierke s disease nonspecific myocarditis and prolonged ectopic tachycardia

Endocardial fibroelastosis is a collagenous and elastic tissue thickening of the endocardium lining the heart chambers most frequently limited to the left ventricle The etiology is not known fetal endocarditis has been suggested as a possible cause but the evidence is not convincing In some cases the cardiac enlargement is predominantly left ventricular while in others the endocardial sclerosis appears to constrict the left ventricle and lead to right ventricular hypertrophy

Von Gierke s disease is a general metabolic disorder in which glycogenolysis is impaired and intracellular deposits of glycogen are found in the liver kidneys and myocardium Hepatomegaly fasting hypoglycemia and ketonuria are characteristic features

The diagnosis of *nonspecific myocarditis* is based on the microscopic finding of interstitial round cell infiltration often with small areas of necrosis or fibrosis in the myocardium in the absence of infectious or other known causes of myocarditis

Prolonged paroxysms of tachycardia in infants have occasionally been reported as a cause of marked cardiac enlargement and death Although prominent dilatation of the ventricles can occur under these circumstances it is unlikely that myocardial hypertrophy can be attributed to a prolonged rapid heart rate alone

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226 CONGESTIVE HEART FAILURE

T R Harrison and William H Resnik

The patient with cardiac disease may face any one of four major hazards or a combination of them These are (1) inadequate coronary circulation (2) bacterial endocarditis (3) embolic complications and (4) congestive failure The first three of these hazards are dealt with in Chaps 224 145 and 230 respectively and the present chapter is limited to the subject of congestive failure Since the basic mechanisms of congestive failure have been considered previously in Chap 14 the present discussion will deal chiefly with the clinical manifestations and treatment of this disorder Cardiac dyspnea produced by exertion acute pulmonary edema and chronic cardiac dropsy represent different types and stages of heart failure

EVOLUTION

The Senile Heart (Presbycardia) The reserve power of the youthful heart is very great There is ample evidence that the decline in strength which occurs in skeletal muscle as a person becomes older also takes place in cardiac muscle Cardiac output per minute and stroke volume decrease with age and circulation time increases Disorders known to place an unquestionable handicap on the heart may precipitate congestive failure in a patient forty five years of age or older even though the same burden may be tolerated without difficulty by a younger person Thus slight elevations of arterial pressure mild forms of thyrotoxicosis and paroxysmal tachycardia of relatively moderate duration may be associated with congestive failure in elderly persons although much more intense examples of the same disorders rarely bring about failure of the myocardium in young individuals The diminishing capacity of the myocardium to cope with these various burdens—organic metabolic or peripheral vascular—as the patient reaches the fifth or sixth decade of life is not due to a reduction in the blood supply to the myocardium when the coronary arterial system is not greatly involved Careful quantitative observations on the perfusibility of the aging heart have demonstrated that aside from diminution in the blood supply to the myocardium due to gross narrowing of the larger branches of the coronary system there is no reduction in the vascular bed that can afford a satisfactory basis for the congestive failure that may have been present during life

This loss of adaptive capacity of the aging myocardium is due to involutionary changes for which there is no recognized histologic basis and the biochemical defect is as yet unknown When these involutionary changes have progressed to the point where they cause or contribute in a significant degree to the appearance of heart failure the authors believe that the most appropriate designation for the condition is *the senile heart* which indicates the loss of cardiac reserve as the result of aging

When elderly persons dying of cardiac failure are found to exhibit lesions known to be well tolerated by younger persons it does not necessarily follow that these lesions *were the sole cause of* the heart failure ultimately causing death It is more likely that subtle senile changes superimposed on these various other lesions have converted them from tolerable into intolerable burdens on the heart *It is essential to appreciate the role that involutionary changes in the myocardium play in reducing the adaptive capacity of the aging heart in coping with the various handicaps to which it is subjected*

In a few elderly persons dying of congestive failure no significant cardiac lesions other than hypertrophy and dilatation are encountered at autopsy The coronary arteries display slight atheroma without narrowing myocardial scarring is minimal the valve cusps are normal Evidence of an extracardiac disease which might burden the heart such as thyrotoxicosis is also absent The blood pressure has been followed during life and has never displayed significant elevation In such persons it is likely that the involutionary process in the heart is the sole cause of failure The decline in reserve has become so great that even the normal load has been excessive Thus the *senile heart* has become so weakened that the patient has succumbed to *senile heart disease* More commonly however such a patient will be found to have coronary atherosclerosis In the absence of a history of anginal pain and of large myocardial scars one is uncertain even after autopsy about the relative importance of aging and of coronary disease in the production of the fatal heart failure

The concept of the senile heart was evolved by William Dock The authors consider it of fundamental importance in understanding many aspects of the problem of myocardial failure

Heart Failure with Effort *Manifestations and Diagnosis* The disproportion between myocardial strength and myocardial load leads to dyspnea, which ordinarily appears first during muscular exercise In a few patients undue fatigue is a striking manifestation but in most patients the complaint is that of increasing dyspnea for a given degree of exertion

The patient s age weight in relation to height and exercise habits must be evaluated before it is decided that the shortness of breath is anything other than a normal physiologic phenomenon Likewise the emotional status of the patient must be considered Worry about the presence of a minor valve lesion may lead to a sensation of smothering with the typical sighing which is so characteristic of the anxiety state

Even when an individual s shortness of breath is known to be beyond the physiologic limits it does not necessarily follow that cardiac disease is the cause Frequently emphysema advanced bronchitis or other pulmonary disorders are responsible Less commonly anemia or even general inanition with muscular weakness consequent to any grave constitutional disorder may lead to some shortness of breath The differential diagnosis of dyspnea has been discussed in some detail in Chap 10 but three points merit emphasis here (1) In deciding whether dyspnea is of cardiac origin the presence of clinical electrocardiographic or radiologic evidence of organic cardiac disease is important but not necessarily conclusive (2) The measurement of circulation time is a simple and valuable procedure With the exception of those disorders associated with increased cardiac output (Chap 14) cardiac dyspnea is associated with prolongation of the circulation time through the lungs On the contrary noncardiac dyspnea is usually associated with normal values for the circulation time. (3) In most borderline situations the response to a therapeutic test will supply conclusive information If the dyspnea is of cardiac origin the administration of digitalis and of a mercurial diuretic plus the ingestion of a salt poor diet will usually produce decisive benefit within 3 or 4 days The patient s subjective impression concerning his dyspnea should be supplemented by observation of the breathing after a given exercise and in doubtful instances by measurements of circulation time before and after the therapeutic test

Heart Failure at Rest *Manifestations and Diagnosis* After a period of months or years the patient with cardiac dyspnea tends to progress into a state of frank congestive heart failure (advanced heart failure) At this time symptoms begin to be present at rest In some instances these symptoms are related to congestion of the lungs alone and there is no evidence of systemic congestion The patient then has shortness of breath in the recumbent posture and frequently suffers from paroxysms of dyspnea (see discussion below under Acute Failure of the Left Side of the Heart) The evidences of cardiac enlargement are likely to be clearly apparent and gallop rhythm is the rule Rales at the lung bases will usually be found but their absence does not exclude the presence of left sided heart failure associated with congestion but without edema of the lungs Some patients display hydrothorax at this time but in most instances this complication occurs later as general anasarca begins to appear

The clinical picture of left sided failure is usually so distinctive as to offer little problem in diagnosis In doubtful instances measurement of the circulation time and observation of the response to digitalis will usually remove all doubt

Eventually the pattern of right sided heart failure develops In some instances this does not appear until the patient has already experienced the phenomena of left sided failure for some weeks or months However occasionally the two sides of the heart appear to fail at about the same time The usual signs of right sided failure are distention of the veins associated with increased venous pressure the presence of an enlarged tender and often painful liver edema albuminuria, and frequently cyanosis Hydrothorax is usually present when there is failure of both sides of the heart and is of great practical importance because of the relief that frequently follows removal of fluid Characteristically the right pleural cavity is affected more frequently than the left Some investigators have ascribed the greater frequency of right hydrothorax to anatomic features such as the position of the left auricle in relation to the two lungs or the right sided course of the azygos vein Others have been impressed by the tendency of patients with heart failure to lie on the right side more than on the left

Ascites is present in almost all instances of advanced right sided failure and under certain circumstances may be out of proportion to the fluid accumulation elsewhere This is seen frequently in children in patients with constrictive pericarditis and in patients with rheumatic disease affecting the tricuspid valve Patients with mitral stenosis may also exhibit prominent ascites with only slight edema of the legs This is probably to be ascribed to anatomic changes in the pulmonary arterial branches with secondary mechanical limitation of congestion and edema of the lungs Thus orthopnea is minimal and the effect of gravity on the distribution of dropsical fluid is less pronounced than in most instances of congestive failure

The clinical picture of a patient with right sided failure or with combined failure of the left and right sides of the heart is so characteristic that ordinarily there will be no difficulty in recognizing it

Other disorders such as cirrhosis of the liver and thrombosis of the hepatic veins (Chiari's syndrome) which may produce enlargement of the liver and ascites are not associated with elevation of venous pressure in the arms unless congestive failure is also present Obstruction of the superior cava may lead to striking distention of the veins of the neck and chest with edema of the upper part of the body However the evidences of collateral circulation are usually outspoken Edema due to renal disease to hepatic disorders or to rarer causes can usually be readily differentiated from the edema due to heart failure by the absence of venous distention of rales in the lung bases of orthopnea etc

In a few patients the pain consequent to hepatic congestion may lead to confusion with primary intraabdominal disorders This error can be avoided by a thorough examination of the circulatory system as well as of the abdomen

Many patients without cardiac failure display prominence of the cervical veins when recumbent Distention of these veins is indicative of increased venous pressure only when it is present in the sitting or semisitting position In doubtful instances the demonstration that compression of the upper abdomen causes marked distention of the cervical veins may be helpful Patients who are recovering from cardiac failure may not have elevation of venous pressure Likewise individuals in whom heart failure develops very suddenly without sufficient time for compensatory elevation of blood volume may have no measurable increase of venous pressure despite marked edema of the lungs In other patients with rapidly developing failure there may be distention of the central and cervical veins with collapse (or constriction) of the peripheral veins As a rule however this function is elevated in individuals with failure of the right side of the heart

Progression of Heart Failure The advance from the early stage with dyspnea only on effort to the full blown picture of combined left and right sided failure may occur gradually over a period of years even though there is no evidence of increasing load In such an instance loss of myocardial reserve as the result of the aging process is probably responsible More commonly however progression tends to occur in a jerky stepwise fashion rather than in a slow continuous evolution Anything which accelerates the heart rate or increases cardiac output is likely to precipitate the next stage of heart failure Thus any ectopic tachycardia may precipitate grave heart failure in a person with diminished cardiac reserve due to disease or age Also important are other causes of tachycardia such as fever from any cause respiratory infections with severe coughing excessive physical exertion prolonged and severe emotional stress anemia consequent to concurrent disease in other areas pregnancy and especially pulmonary infarction Another frequent aggravating cause of heart failure is the excessive ingestion of salt The prevention and management of these factors which constitute one of the most important general principles in the treatment of congestive failure are discussed later

COMMON CLINICAL PATTERNS

There are a number of situations in which the heart fails suddenly They include myocardial infarction fulminant myocarditis certain ectopic tachycardias and various rarer disorders These several types of acute cardiac failure are associated with evidence of minimal systemic congestion because they set in so rapidly that there is not time for compensatory increase in blood volume to occur Hence these conditions are likely to be characterized by a shift of blood from one portion of the circulation to another and in most instances the clinical picture mimics that of peripheral circulatory failure or shock the manifestations of congestion being limited to the pulmonary vascular bed This type of sudden cardiac failure has been discussed in Chap 14 and need not be considered further here However there is one form of acute heart failure which merits detailed discussion because of its frequency and of its response to therapy This is the condition known as *cardiac asthma* or *acute pulmonary edema*

Acute Failure of the Left Side of the Heart (Paroxysmal Nocturnal Dyspnea Cardiac Asthma and Acute Pulmonary Edema) Patients with hypertension with lesions of the aortic valve and with coronary sclerosis frequently are awakened by seizures of dyspnea Various names have been applied to these episodes The severe and fatal instances are characterized by acute edema of the lungs In many of the patients the moist rales are limited to the bases and the physical signs are chiefly those of bronchial obstruction with wheezes and rhonchi It is probable that edema of the bronchial walls is especially important here although some believe bronchospasm to be concerned When the number of moist rales is limited in relation to the wheezes and squeaks the condition may be confused with bronchial asthma or with other causes of wheezing Since the episodes usually occur at night the term *paroxysmal nocturnal dyspnea* has been widely employed but it has the disadvantage that similar episodes may occur during the day and that other diseases such as bronchial asthma occasionally cause paroxysmal dyspnea at night From the standpoint of tradition there is some advantage in retaining these several terms provided it is clearly understood that they all refer to one fundamental dis

order—acute failure of the left side of the heart

There is strong evidence that these seizures of dyspnea are usually precipitated by various conditions which lead to an increased return of blood to the heart Of particular importance are the recumbent posture and the associated reabsorption of extracellular fluid from the dependent portions of the body into the blood stream This leads to a situation analogous to that induced by the administration of saline solution to the patient Less important precipitating factors are cough nightmares excessive warmth and possibly abdominal distention Ordinarily they represent only the final straws which may awaken the patient or exaggerate the effects of the reabsorbed fluid

In a typical instance the patient who has previously had some shortness of breath on effort but no symptoms at rest retires for sleep in his usual state of health After an hour or more he is awakened with a sense of suffocation sits up and may seek an open window At the same time there is some coughing and examination of the lungs at this period will reveal a few moist rales at the bases and scattered squeaks over the lung fields In most instances the attack subsides after a few minutes of panting and coughing in the upright position However in the more severe attacks the dyspnea becomes progressively worse the cough more severe and there is expectoration of copious frothy sputum tinged with blood Examination reveals scattered wheezes and squeaks and in addition moist rales all over both lung fields This is acute pulmonary edema which may be fatal within an hour or two unless appropriate therapy is promptly instituted

Typically these seizures occur in patients with left ventricular failure due to hypertension lesions of the aortic valve or myocardial disease The first episode may be initiated by a myocardial infarction which may be painless In such instances the seizure is induced by sudden decrease in myocardial strength rather than by rapid increase in the load on the heart which is the more common mechanism

Attacks of dyspnea which awaken the patient from sleep are rather uncommon in patients with mitral stenosis except when precipitated by auricular fibrillation or pulmonary infarction However persons with mitral stenosis may suffer from acute pulmonary edema precipitated by exertion or even by recumbency In the latter instances the attacks usually begin before the onset of sleep

Patients with the milder episodes of acute left ventricular failure awaken assume the sitting or standing position and relieve the attack within a few minutes However the severe form of this syndrome represents one of the gravest of all medical emergencies Most patients with acute pulmonary edema will survive if therapy is prompt and vigorous Without such therapy many of them will die

Treatment The initial step should be the administration of morphine or an allied drug The benefit resulting from respiratory depressants is probably due to the effect of these drugs in breaking the vicious cycle whereby dyspnea itself a result of congestion of the lungs leads to reduction of mean intrathoracic pressure which causes greater inflow into the right ventricle and increase in the severity of the congestion when the left ventricle is less able to propel the blood offered to it Thus dyspnea causes more congestion which causes more dyspnea and so the vicious cycle proceeds until the respiration is depressed by a drug of the morphine group

Reduction of venous return to the right side of the heart can be accomplished to some extent by venostasis which consists in applying tourniquets to three extremities Every few minutes a tourniquet is placed on the fourth extremity and one of the others is released Thus the danger of thrombosis is minimized In the severer instances venesection should be employed and one should not hesitate to withdraw as much as a liter of blood in successive bleedings of 500 300 and 200 ml

Oxygen is urgently needed in patients with acute pulmonary edema Details concerning its administration are presented in Chap 273

When patients who have not received digitalis develop acute pulmonary edema the rapid acting digitalis preparations must be administered immediately Digitalis lanata (Cedilanid) should be given intravenously The total dose for a patient not previously receiving digitalis is usually 1 2 to 2 0 mg, which may be given over a period of 2 hr or less in urgent instances The initial dose should be 0 8 mg and subsequent doses of 0 4 mg may be given at half hourly intervals

When a patient has already been receiving digitalis the problem is more difficult Once it has been determined that the patient is only partially digitalized then Cedilanid should be used with caution in an initial dose of 0 4 mg followed by 0 2 mg at half hourly intervals until improvement occurs or evidence of digitalis intoxication appears

In the *prevention* of attacks of acute pulmonary edema the following principles of therapy are important (1) The maintenance of adequate digitalization (2) The treatment of extracellular fluid excess even though there may be no detectable pitting edema This involves the utilization of mercurial diuretics and restriction of sodium chloride (3) Every attempt should be made to avoid the precipitating factors A patient who has been having attacks of acute pulmonary edema should sleep in the semisitting position and should have a special bed when this is available Mild sedatives should be administered to minimize disturbing dreams Cough and emotional stresses should be

controlled so far as possible The evening meal should be small in order to minimize cardiac work When the condition recurs repeatedly a responsible member of the family should be instructed in the administration of morphine or an allied drug as soon as the attack begins Otherwise the patient may succumb before the physician can reach the bed side

To summarize attacks of pulmonary edema can be best prevented by vigilant and vigorous application of those therapeutic procedures which are used to treat heart failure in general and which are discussed later in more detail

Disorders other than left sided heart failure may cause acute pulmonary edema It may occur in patients with inspiratory obstruction presumably the lowered intrathoracic pressure favors transudation of fluid from capillaries into the alveoli If the obstruction is in the larynx tracheotomy may be of great benefit If the obstruction is lower in the bronchial tree bronchodilator drugs or antibiotics may be helpful depending on the cause

Pulmonary edema may be caused by inhalation of irritating gases or particulate matter Cessation of contact with the irritating agent is of course the first indication in management

Acute pulmonary edema may develop following severe brain injury e g in massive intracerebral or intraventricular hemorrhage or in bulbar poliomyelitis The mechanism is not well understood and little can be done to alleviate the situation

Oxygen therapy (p 1773) may be expected to be of assistance in any type of pulmonary edema where there is arterial unsaturation If equipment is available additional benefit may be obtained by administering the oxygen under positive pressure Agents which lower surface tension may be of value as adjuncts to oxygen in cases where there is a considerable quantity of foamy sputum The simplest method of achieving this is to bubble the oxygen through 95 per cent ethyl alcohol

Gravely ill comatose patients often exhibit coarse and rattling respiration This does not represent true pulmonary edema but instead is due to accumulation of mucus in the bronchi because of muscular weakness and depression of cough reflexes

Periodic Breathing In elderly persons with failure of the left side of the heart periodic breathing (Cheyne Stokes respiration) may be accompanied by recurrent brief episodes of dyspnea The same patient may have this periodic dyspnea as he dozes off to sleep and then be awakened by acute pulmonary edema More commonly a patient has only one of these syndromes The treatment of nocturnal dyspnea due to Cheyne Stokes respiration is essentially that of heart failure in general However opiates should be used sparingly and the milder sedatives are often efficacious This type of dyspnea usually indicates a poor prognosis but unlike acute pulmonary edema does not constitute a grave emergency

Chronic Congestive Heart Failure The majority of patients who have chronic heart failure have failure of both sides of the heart All the manifestations of both right and left sided failure are present in many patients but some of them present only a portion of these manifestations such as edema without detectable hepatic enlargement or the reverse situation Other patients will have right sided hydrothorax with no other evidences of failure of the right ventricle In such instances it is uncertain whether the accumulation of fluid in the pleural cavity comes from the visceral pleura and is a manifestation of left sided failure or whether it arises from the parietal pleura and is the result of early right sided failure The rarity of hydrothorax in patients with failure of one side of the heart only and its frequency when left and right failure coexist suggest that congestion of both parietal and visceral pleura may be necessary for its development

It should be emphasized that slight pitting of the ankles at the end of the day occurs in many healthy people Individuals who have lost weight frequently have a palpable liver Elderly persons who are leading a sedentary life are often short of breath on exertion Emotional disturbances may rarely cause episodes of shortness of breath (usually described as smothering) at night Thus there may be some doubt in a borderline situation as to whether a patient does or does not have cardiac failure In such an instance observation of the response to a mercurial diuretic and to digitalization will usually supply conclusive evidence When the symptoms mentioned are not due to cardiac disease little or no improvement will be noted and even this will be mainly the result of suggestion When however such apparently minor symptoms are in reality the earliest indication of myocardial failure the administration of digitalis to a patient who has not previously received it and of mercurial diuretics will usually result in such striking improvement as to remove all doubt from the physician s mind Actually in most instances such a therapeutic test is not necessary because the presence of a diastolic gallop will often settle the question conclusively However one should remember that the presence of objective evidence of cardiac disease such as an organic murmur or an unquestionable abnormality of the electrocardiogram does not necessarily mean that the symptoms are the *result of cardiac disease* Individuals with such minor cardiac abnormalities may have symptoms which are the result of coexistent emotional or physical disorders In such persons impressive re

sponses to digitalis and diuretics will not be observed

It should be emphasized again that the diagnosis of congestive failure must not be based on any one manifestation but rather on a combination of them Thus enlargement of the liver and ascites may be the result of cirrhosis and an almost identical picture may be caused by constrictive pericarditis In the latter instance there will be increased pressure in the cervical veins and in those of the upper extremities such manifestation being absent in patients with cirrhosis Likewise mediastinal tumors may be associated with increased pressure in the veins of the neck and of the arms but evidence of congestion in the lower part of the body will be absent

Edema due to renal disease is associated with characteristic changes in the urine The changes are either those of the nephrotic syndrome with massive albuminuria or of acute glomerular nephritis with hematuria and cellular casts Hypoproteinemia is frequently present in minimal degree in patients with chronic cardiac edema but rarely approaches the low values observed in patients with nephrosis and cirrhosis Patients with acute glomerulonephritis often have both cardiac and renal factors present and operative in the causation of edema The presence of dyspnea hypertension cardiac enlargement and gallop rhythm will usually be sufficient to indict the heart as one factor in the production of edema

Prognosis is uncertain in patients with chronic cardiac failure One cannot predict when massive pulmonary infarction a severe intercurrent infection or cerebral vascular complications will occur Despite such uncertainties three factors are of particular importance in prognosis The first is the response to therapy The failure of impressive improvement to set in within a few days following vigorous therapy is likely to indicate a grave outlook

The second factor is the type of underlying cardiac disease When the congestive failure is basically the result of a mechanical lesion such as tricuspid stenosis mitral stenosis or constrictive pericarditis the prognosis is likely to be much better than when the clinical manifestations are the result of a failing myocardium It is the latter which is responsible for heart failure in patients with coronary artery disease and in those with hypertension and aortic valvular disease Although these latter individuals have a mechanical burden symptoms do not occur until the left ventricular myocardium has lost its reserve On the other hand, the pulmonary manifestations of mitral stenosis are dependent on a purely mechanical disorder as are the systemic congestive manifestations of tricuspid stenosis Therefore patients with heart failure due to stenosis of the auriculoventricular valves may live for many years in a state of semiinvalidism This is rarely the case when as the result of disease or of the mechanical load the myocardium has to become defective before heart failure develops

A third important factor in prognosis is the evaluation of the circumstances under which heart failure develops When it has occurred as the result of some circumstance that is particularly amenable to treatment or correction such as auricular fibrillation with a rapid rate or respiratory infection or undue exertion or the excessive ingestion of salt the prognosis is likely to be much better than when heart failure has developed in the absence of any such additional stress In the final analysis however the response to treatment is the single most important point in prognosis

TREATMENT OF CHRONIC CONGESTIVE HEART FAILURE

Prevention and Management of Aggravating Factors The clinical state of patients with chronic cardiac disease does not progress steadily downward but tends to remain stationary or improve slightly for long periods of time with sudden worsening as the result of various complications Most of these complications are conditions which cause acceleration of the heart rate and/or increased output Ectopic tachycardias with extremely rapid rates may precipitate failure in individuals with previously good myocardial reserve However when the reserve power of the heart is much diminished even slight degrees of sinus tachycardia may exert deleterious effects Respiratory infections with the associated distressing cough physical exertion beyond that which produces dyspnea fever due to any cause emotional stress and anemia are particularly important in this respect The therapeutic implications are obvious

Pulmonary infarction discussed in Chap 236 is one of the commonest complications Its likelihood can be reduced by avoiding excessive rest in bed by permitting some slow walking by elastic bandages by alertness in the detection of phlebothrombosis and by the use of anticoagulants in appropriate instances

In patients with cardiac disease *pregnancy* involves a number of special problems which are discussed later

Rest and Activity The initial consideration in the management of the patient with congestive failure is that of placing him in a position in which dyspnea and the consequent metabolic demands on the heart are minimal In most patients the semirecumbent position in bed meets these requirements The upright posture favors edema formation in the dependent portions of the body but tends to diminish

pulmonary edema a far more serious condition than peripheral edema

Ordinarily the patient with congestive failure should be allowed to get out of bed and walk to a nearby commode for bowel movements This procedure has the additional advantage of tending to exercise the leg muscles and thereby reduce the likelihood of phlebothrombosis and pulmonary infarction When for any reason the patient s strength does not permit being out of bed and walking a little each day anticoagulant drugs elastic stockings and passive exercises of the legs plus massage are indicated

The great advantages of the recumbent position are in lessening fatigue and in combating peripheral edema and the subsequent rapid resorption of fluid during the night with the danger of inducing paroxysmal dyspnea Hence there is some advantage in attempting to induce diuresis by having the patient assume the horizontal position for several hours a day preferably in the late afternoon or early evening When this daily rest period induces diuresis it should be carried out indefinitely as long as the activities of the day in the upright position result in the development of more than a slight amount of edema of the lower extremities

Diet and Fluids All patients with heart failure should be placed on a low sodium diet the extent of the sodium restriction depending on the severity of the cardiac failure With the elimination of salted foods the use of sodium free milk bread and butter and the avoidance of canned vegetables and prepared condiments diets containing not more than 200 to 400 mg sodium per day can be administered At the same time it is important to be certain that the water ingested (especially if it is water that has been softened) is poor in sodium and that drugs containing sodium are avoided This extremely unpalatable type of diet is necessary only for patients with advanced heart failure In milder instances diets containing 1 0 to 2 0 Gm sodium (2 5 to 5 0 in salt) may be permitted

When the patient with congestive failure is first seen anorexia may be so severe as to preclude a reasonably well balanced diet Under these circumstances sodium free milk (Lanalac) or fruit juices alone containing only minute quantities of sodium are preferable to the traditional Karell diet (800 ml milk per day containing about 400 mg sodium) for the first 2 or 3 days At the end of this time and as the result of this regime and other therapeutic measures simultaneously instituted it is usually possible to administer a balanced diet containing not more than 200 to 400 mg sodium (equivalent to about 0 5 to 1 Gm sodium chloride) When compensation is fully restored or when the maximal therapeutic effect has been achieved some of the dietary restrictions may be lifted However it is preferable to insist that the patient remain permanently on a diet containing not more than 1 000 to 2 000 mg sodium and considerably less in the case of those individuals whose myocardial efficiency is markedly impaired The less the sodium intake the less the tendency for outspoken congestive failure to recur and the less the need for mercurial diuretics

The intake of water should usually be regulated by the desire of the patient

Weight reduction is desirable for obese patients and thiamine is indicated when there is protracted anorexia even of mild degree The other vitamins may be given also when the anorexia is both prolonged and severe

Digitalis Since this drug constitutes one of the cornerstones of management it will be discussed in some detail

Mode of Action The main effect of digitalis appears to be strengthening of the cardiac muscle with increase in ventricular emptying Thus the drug tends to overcome the cardinal hemodynamic defect of myocardial failure which is defective emptying of the ventricles (Chap 14) In patients with auricular fibrillation digitalis causes additional benefit by producing pronounced slowing of the ventricular rate by reducing the responsiveness of the junctional tissues to the barrage of impulses arising in the atrium The slowing of the rate is slight in patients with regular rhythm and appears to be of vagal origin

Indications Auricular fibrillation with a rapid ventricular rate constitutes one of the chief indications for digitalis When the drug is given intravenously as lanatoside C (Cedilanid) and when the arrhythmia is of the paroxysmal type and of short duration normal rate and rhythm are restored in some patients However this happens more frequently in patients with paroxysmal tachycardia *In chronic auricular fibrillation the drug slows the rate without abolishing the abnormal auricular rhythm* Digitalis frequently converts auricular flutter into auricular fibrillation Therapeutic doses will abolish premature beats in many patients with cardiac failure Toxic doses produce premature beats often in the form of bigeminal rhythm Further details concerning digitalis and arrhythmias will be found in Chap 223

The most common indication for digitalis is the presence of congestive heart failure even when the rhythm is regular When failure is severe the drug alone is often ineffective and other measures such as diuretics are needed However in the earlier instances and especially in those having attacks of paroxysmal nocturnal dyspnea digitalis alone is usually efficacious in treating and preventing the seizures

The drug should be used in patients with early

failure when the cardiac reserve is diminishing as indicated by increasing dyspnea for a given effort or by well marked gallop rhythm

In doubtful instances the value of the drug can be tested by clinical observation of the response supplemented at times by measurement of vital capacity and circulation time before and after digitalization This procedure is occasionally of value in differentiating dyspnea due to cardiac disease from that due to emphysema and other pulmonary disorders As a rule a patient should be given digitalis when the minimal exertion which can be carried on while leading a reasonably active life begins to induce dyspnea

Once digitalis has been administered for congestive failure the patient will usually need it either continuously or for long intervals throughout most of his life The practice frequently followed of discontinuing the drug as soon as the overt manifestations of congestive failure have disappeared is not sound

In some patients with paroxysmal auricular tachycardia the seizures are prevented by the daily administration of digitalis in other instances this procedure is ineffective

Contraindications This drug like any other is contraindicated under conditions where there is no clear indication for its use Neither enlargement nor murmurs constitutes an indication unless there is dyspnea or edema It should not be given to people with sinus tachycardia except when clear evidence of congestive failure either actual or imminent is present

Digitalis may cause nodal or ventricular tachycardia and most instances of fatal digitalis intoxication arise from the mistaken assumption that the presence of tachycardia in such patients constitutes an indication for larger doses Bradycardia of moderate degree is often a desirable effect and the common practice of discontinuing the drug when the heart rate is less than 70 per minute is unsound In some patients maximal benefit is achieved at rates between 50 and 60

Preparation and Dosage If one form of digitalis administered properly fails to produce improvement it is unlikely that significant benefit will be obtained by a different preparation The best results will usually be achieved by the physician who familiarizes himself thoroughly with only two preparations one a rapid acting type for emergencies and the other an intermediate or long acting product for long term digitalization

The idea that all patients require about the same dosage of digitalis is mistaken Actually there are wide variations The powdered leaf about 1 2 to 1 6 Gm in 48 hr and gitalin (Gitaligin) about 5 to 7 mg in 48 hr are excellent preparations for most patients who have not been previously receiving the drug When there is no emergency the best procedure is to give a patient about two thirds of the minimal digitalization dose in the first 24 hr If such a dose causes no improvement it is unlikely that digitalis will be of much value If the expected benefit has been achieved the maintenance dose may be instituted without proceeding to "full digitalization If the degree of improvement is less than anticipated the average maintenance dose may be given three times daily after meals for several days and then twice daily after meals The patient should be instructed not to take the drug unless the meal has been eaten and enjoyed In this way the onset of anorexia which is usually the initial manifestation of toxic effects tends to limit the dosage of the drug The usual daily maintenance dose is about 0 5 mg gitalin 0 1 mg digitoxin or 0 1 Gm powdered leaf

Many physicians prefer to use digitoxin because the available knowledge concerning its absorption excretion and destruction appears to be more precise than in the case of other preparations Such knowledge indicates that about one half the daily administered dose is excreted daily and that the destruction is largely independent of dosage and proceeds at a fixed rate for a given patient If the sum of excretion and destruction is greater or less than the daily intake the patient will eventually lose the digitalis effect or develop digitalis intoxication It is probable that the same principles apply to other digitalis preparations and if so it is theoretically impossible to maintain a patient in a properly digitalized state on a constant daily maintenance dose unless it is almost exactly equal to the sum of the daily excretion and destruction This dilemma may be avoided by routinely utilizing the average maintenance dose (Table 114) or slightly less of one of the intermediate preparations (digoxin or gitalin) and giving augmentation doses for a few days every 2 or 3 weeks At this time the patient must be seen by the physician in order to be certain that bigeminal rhythm and other manifestations of digitalis toxicity are not present In their absence the patient is instructed to take the previous daily maintenance dose three times daily after meals and only provided the appetite has not suddenly declined This procedure is continued until either (1) anorexia and/or nausea develops (2) the physician who should see the patient daily during this period of augmented dosage detects frequent premature beats or (3) the desired clinical improvement occurs In the latter instance there is no need to continue to the point of toxic effects Many patients do not require complete digitalization and will improve on this plan without untoward effects However if a constant daily dose of any preparation is employed indefinitely a large percentage of patients will

Table 114 DIGITALIS THERAPY

Preparation	Chief indication	Route of administration	Total dose for optimal initial effect	Optimal period for initial digitalization	Dissipation time		Usual maintenance dose	Remarks
					For toxic effects	For all effects		
Lanatoside C (Cedilanid)	Acute pulmonary edema myocardial infarction with failure	Intravenous or intramuscular	1 0–2 mg	2 12 h	1 day	4 7 days	Not employed	
Digoxin	Chronic heart failure	Oral	1 5– 5 mg	48 hr	3–4 days	6 8 days	0 5 mg	
Gitalin (Gitaligin)	Chronic heart failure	Oral	5–7 mg	2–5 days	1 3 days	5 10 days	0 5 mg	To arrive at full digitalization slowly use one-fourth optimal initial dose daily until desirable or toxic effects occur
Powdered leaf	Chronic heart failure	Oral	1 0–1 6 Gm	3–6 days	7 days	10 14 days	0 1 Gm	
Digitoxin	Chronic heart failure	Oral	1 0 1 6 mg	3–6 day	3 10 day	1 0 day	0 1 mg	
Acetylstrophanthidin *	To determine whether patient is digitalized *	Intravenous	0 2 mg every 5 min until toxic effects occur	Few minutes	Few minutes	2 hr		Appearance of toxic effects after 0 2 0 4 mg = preexisting digitalis intoxication 1 0 1 mg = not previously digitalized

* The use of this drug may be hazardous and its only value is in determining whether the patient needs additional digitalis In most instances this can be safely determined by omitting the drug for a few days.

eventually exhibit such effects or become completely undigitalized If this method is used the intermediate preparations are decidedly preferable both for maintenance and for augmentation because intoxication of mild degree frequently occurs during the periods of augmentation and the duration of such intoxication is less than when digitoxin or powdered leaf is employed

When a rapidly acting digitalis is desired or when one is uncertain as to whether or not the drug should be given and wishes to use a preparation the effect of which will wear off within a few days *Digitalis lanata* may be administered intravenously The most satisfactory preparation of *Digitalis lanata* is lanatoside C (Cedilanid) Its quick onset of action makes it especially valuable in the management of such emergencies as acute pulmonary edema Its rapid disappearance from the body makes it useful in patients who need digitalis but who are particularly susceptible to its untoward effects Hence in a person with myocardial infarction and increasing congestive failure in whom digitalization may precipitate a serious disturbance of rhythm this drug is preferable to powdered leaf or gitalin On the other hand the rapidity of elimination makes it less desirable for use in the management of the usual patient with congestive failure The usual total dose of lanatoside C required for digitalization is 1 to 2 mg for adults This is administered intravenously in divided doses over a period of 4 to 8 hr When good response is obtained a longer acting preparation should be used to maintain the effect Since lanatoside C is rapidly dissipated this can be accomplished by giving gitalin 0 5 mg three times daily after meals for about 5 days and then 0 5 mg once daily indefinitely The drug is temporarily *discontinued if the appetite is lost or nausea develops* In the above plan one may substitute 0 1 mg digitoxin or 0 1 Gm powdered leaf for 0 5 mg gitalin The administration of the longer acting preparation is begun about 8 to 12 hr after the final dose of Cedilanid

In patients who have been receiving digitalis and who have nausea and vomiting it may be difficult to decide whether these symptoms are the result of abdominal congestion and constitute an indication for additional digitalis or whether they represent *toxic effects from overdosage* Under such circumstances the use of acetylstrophanthidin has been proposed However this is a hazardous procedure In the usual patient the same information can be obtained by stopping digitalis therapy for a few days and noting whether the clinical state improves as will occur if digitalis intoxication has been present

In Table 114 the more pertinent information concerning a number of digitalis preparations is summarized

Manifestations of Digitalis Intoxication The most important of these include gastrointestinal disturbances—i e anorexia nausea and vomiting developing in that order—and disturbances of the

cardiac rhythm of which the frequent premature beat usually in the form of bigeminal rhythm is the most common Inversion of the T waves and slight increase in the P R interval are normal effects of the drug Severe degrees of heart block due to digitalis intoxication are exceptional in man although they occur frequently in animals when excessive doses are administered In an occasional patient the drug converts sinus rhythm into auricular fibrillation The reverse effect—conversion of auricular fibrillation to normal rhythm—may occur when the arrhythmia is of recent onset Nodal rhythm with moderate to marked tachycardia occasionally appears and ventricular tachycardia may develop with danger of ventricular fibrillation if the administration is continued Less common toxic effects include diarrhea and xanthopsia (yellow vision)

When doses within the therapeutic range are employed the only common toxic effects are anorexia nausea and bigeminal rhythm all of which disappear within a few days after withdrawal of the drug Since it is often desirable that the drug be pushed to the onset of the minor toxic effects it is well to warn the patient that vomiting may occur Such warning not only will alleviate anxiety if vomiting does appear but will make the patient more alert to report the onset of anorexia which is usually the initial and the most benign indication that the toxic effect has developed However it is important to remember that the more serious toxic effects may supervene without the preliminary appearance of the usual warning signals in the form of the milder manifestations of toxic action

Premature beats or other arrhythmias when induced by digitalis may be improved by the oral administration of potassium salts (Chap 223) Such arrhythmias are especially likely to be caused by digitalis when there is potassium depletion as the result of the frequent use of mercurial diuretics Since glucose ingestion causes decline in plasma potassium the toxic arrhythmias due to digitalis should be sought especially carefully during the period of 30 to 60 min after a carbohydrate rich meal When digitalis intoxication is present or imminent protein rich carbohydrate poor meals are indicated and potassium chloride (1 Gm three to six times daily) should be administered orally unless renal insufficiency is present

The most important principle of digitalis therapy is to push the drug until the patient exhibits either the desired therapeutic action or definite evidence of toxic effects This is only another way of saying what William Withering who introduced the drug into medical practice stated so clearly Let the medicine be continued until it either acts on the kidneys the stomach the pulse or the bowels let it be stopped upon the first appearance of any of these effects

Diuretic Drugs These are of great value All patients who have ever suffered from edema of cardiac origin and who have a tendency toward recurrence should weigh themselves each day under standard conditions As a rule this means weighing in the morning immediately after rising and emptying the bladder without clothing other than slippers and pajamas The written record of such daily weighings constitutes the guide to therapy by diuretic drugs

The mercurial diuretics are the most effective and their administration often results in striking improvement There is evidence that these drugs act by diminishing the reabsorption of chloride (and/or sodium) in the renal tubules such an effect being brought about by temporary depression of renal enzyme systems The volume of diuresis is usually greater if these drugs are given to patients who are concurrently receiving ammonium chloride 1 Gm (15 gr) three times daily The ammonium salts may produce acidosis if employed for more than a few days at a time Unless renal function is seriously impaired it is well to administer potassium chloride (3 to 4 Gm per day) routinely and to add ammonium chloride for 3 days when a mercurial diuretic is to be administered

Opinions differ concerning the mercurial diuretic of choice Convincing evidence that any one of the currently available preparations is superior to the others is lacking The size of the dose and the frequency of administration are governed by the severity of the congestive failure the rapidity with which its manifestations occur and the response in the individual case The initial dose should be 1 ml intramuscularly if no untoward symptoms are produced and a loss of 2 to 3 lb in the course of 24 hr is effected the same dose may be given daily for a few days or at longer intervals depending on the urgency of the case If a satisfactory diuresis is not produced by 1 ml 2 ml is given and this dose may be repeated after several days The mercurial is administered until all evidences of passive congestion have disappeared and the weight becomes stabilized at a steady level When compensation has been restored a maintenance dose of the mercurial is administered at varying intervals using the weight curve as the guide The patient should be instructed to report to the physician whenever the weight increases by as much as 5 lb within a period of 1 or 2 weeks or if a lesser gain in weight is attended by increase in dyspnea

The response to mercurial diuretics may be potentiated in some patients by administering am

nophylline intravenously (0 5 Gm over a 5 min period) 2 hr after the previous injection of the mercurial This synergistic effect is ascribed to the increase in glomerular filtration produced by the aminophylline while tubular reabsorption of chloride and of sodium is inhibited by the mercury compound

In many patients oral mercury is effective One to three tablets of chlormerodrin (Neohydrin) may be given after each meal Untoward effects may consist of gingivitis especially in patients with poor oral hygiene nausea and diarrhea Some patients respond well for many months but this is an expensive method of therapy

The untoward effects of mercurial diuretics fall into several categories the most important being those related to *electrolyte depletion* of different types These electrolyte disturbances are likely to occur in persons whose salt intake has been severely restricted and who have received vigorous mercurial therapy with massive diuresis Aside from refractoriness to further injections of mercurials there may be no symptoms or there may be a group of symptoms common to all regardless of the electrolyte patterns lassitude apathy mental confusion anorexia decrease in urine volume and azotemia When adequate facilities are available frequent measurement of the serum levels of sodium potassium chloride and carbon dioxide as well as of urea should be carried out especially when repeated injections of mercurials are necessary and when congestive failure does not respond to adequate therapy

The *low salt* or *salt depletion* syndrome is present when excessive sodium and chloride losses are disproportionately greater than those of water and when there is a corresponding lowering of these electrolytes in the serum When water sodium and chloride are excreted in excessive quantities and in ratios similar to those that obtain in the normal serum a volume deficit will ensue even though the plasma electrolyte pattern remains in the normal range and despite the persistence of edema in the dependent parts The treatment consists of the addition of salted foods or of salt rich bouillon to the diet or in more urgent cases by the slow infusion of 200 to 300 ml of 5 per cent sodium chloride on two or three successive days

The *salt dilution syndrome* presents the same electrolyte pattern with low sodium and chloride levels but this condition appears to develop through a different mechanism and to have a different significance It is encountered in the late stages of heart failure as well as in a variety of other unrelated terminal illnesses even when there have been no unusual losses of salt Hypertonic sodium chloride is rarely of benefit in these patients and although the plasma electrolyte pattern may be temporarily corrected thirst is aroused further excesses of water are retained the serum sodium and chloride levels fall to their previous levels and the net result is an increase in the extracellular fluid volume with further increase in edema Differentiation of the salt depletion from the salt dilution syndrome is sometimes difficult or impossible and the therapeutic test of the cautious administration of hypertonic sodium chloride may be required

Another important electrolyte disturbance stemming primarily from mercurial diuresis is *hypochloremic alkalosis* due to the disproportionate loss of chloride and potassium Body stores of potassium are usually depleted even though serum potassium may be normal Serum chloride is abnormally low bicarbonate is correspondingly elevated and sodium remains normal or at near normal levels Exactly the same chemical findings occur in respiratory acidosis and differentiation between the two must be made on clinical grounds unless means for accurate measurement of the plasma pH are available Respiratory acidosis occurs when the primary cause of the difficulty is a pulmonary disorder such as obstructive emphysema interfering with O_2 and CO_2 exchange or a depression of ventilation (e g morphine or sedatives) acting in essentially the same way The treatment of hypochloremic alkalosis consists of the administration of ammonium chloride 4 0 to 6 0 Gm per day in divided doses or when oral administration is not possible by the slow intravenous infusion of a 1 per cent solution of ammonium chloride at a rate not greater than 100 ml per hr Five hundred milliliters may be given on one day and repeated the next if necessary The effect of acetazoleamide (Diamox) is very similar to that of ammonium chloride and the combined effect of acetazoleamide 250 mg t i d and ammonium chloride 4 0 Gm per day may bring about a fairly rapid restoration of chloride to normal levels Potassium chloride 1 0 Gm four times daily should be given orally since a potassium deficit practically always accompanies hypochloremic alkalosis

Potassium deficiency in the absence of alkalosis may occur following the prolonged use of mercurials particularly when there have been additional losses of potassium by vomiting or diarrhea and when anorexia has limited the supply of food The chief manifestations in addition to those described above as being common to all electrolyte disturbances are unusual muscular weakness abdominal distention due to intestinal atony and electrocardiographic alterations progressive depression of the S T segment and rounding lowering and inversion of the T wave increasing amplitude of the U wave in the left precordial leads It is important to bear in

deficits may exist even though the serum potassium level may be normal and such a deficiency should be presumed to exist when ammonium chloride or acetazoleamide has been administered when hypochloremia alkalosis occurs and particularly when unexpected digitalis intoxication develops Consequently 2 or 3 Gm potassium chloride on the day of and the day following a mercurial injection may serve to prevent the appearance of potassium deficiency

Tetany due to loss of calcium is an uncommon complication of mercurial therapy

In patients with prostatic hypertrophy profuse diuresis following mercurial therapy may cause acute urinary retention

Intravenous administration of mercurial diuretics may lead to severe collapse and even to sudden death which is probably to be ascribed to interference with the normal role of sulfhydryl groups in myocardial enzymatic reactions Such very rare reactions do not follow administration by other routes Therefore the intravenous route should not be employed Allergic reactions are exceptional and may usually be prevented by change to a different preparation Acute anuria (lower nephron nephrosis) is very rare and can be largely prevented by measuring at frequent intervals the urea content of the blood and by careful clinical observations especially in relation to the early symptoms (lassitude apathy etc) of electrolyte depletion

Aside from the presence of evidence of the toxic effects which have been mentioned the chief contraindications to the use of mercurial diuretics are (1) failure of diuretic response to previous injection and (2) presence of serious impairment of renal function as indicated by marked elevation of blood urea by fixation of specific gravity of the urine or by the appearance of red blood corpuscles in the urine in large numbers A few red blood corpuscles do not constitute a contraindication nor does proteinuria

Refractoriness to mercurial diuretics represents a common and grave situation It can sometimes be overcome by the production of hyperchloremic acidosis For this purpose ammonium chloride (8 Gm daily in divided doses) is given for 5 days Unless the patient is eating normally potassium chloride (4 to 6 Gm daily) should likewise be prescribed During the first 3 days of the regime acetazoleamide is administered in doses of 250 mg twice daily On the fifth and several subsequent days mercurial diuretics are administered In doubtful instances blood chloride and carbon dioxide-combining power should be measured daily and the acetazoleamide and ammonium chloride administration continued until the respective values are significantly altered In some patients it appears to be necessary to achieve levels of 120 mEq per liter or more for chloride and 20 mEq per liter or less for bicarbonate before the refractoriness can be overcome

There are favorable reports concerning chlorothiazide (Diuril) a new orally effective nonmercurial diuretic Doses of 500 to 1 000 mg twice daily may be administered for several weeks if necessary Toxic effects are apparently minimal or absent while there is enhancement of excretion of sodium chloride and water

Other Therapeutic Measures *Sedatives* The judicious administration of sedatives is helpful especially in the early days of severe congestive failure For dyspnea morphine (10 to 20 mg) or Pantopon (10 to 20 mg) administered parenterally is usually effective in affording some degree of comfort and in ensuring sleep They are best given in the evening and after 4 hr or more repeated once during the night if necessary but always with due regard for the caution necessary in the use of these drugs in the aged and for the dangers of habituation if they are used for more than a few days Aside from promoting sleep opiates are valuable because they reduce the strenuous work of the respiratory muscles They also enable the subject to assume the recumbent position which often initiates diuresis After the first few days when congestive failure has been considerably alleviated moderate amounts of barbiturates may be substituted During the day small doses of phenobarbital (15 to 30 mg) two or three times daily may diminish undue restlessness and apprehension *It is most important however that one be particularly careful to avoid excessive sedation* because of the possibility of rendering the patient so lethargic that he is unwilling or unable to participate in sufficient activity to minimize the danger of phlebothrombosis and because of the undesirability of excessive respiratory depression in a patient with lowered vital capacity

Venesection Seizures of acute pulmonary edema constitute the most important indication for venesection which is a rapidly effective and often a lifesaving procedure under these circumstances (p 1307) Venesection is usually beneficial in patients with chronic cor pulmonale who have hematocrit values of 50 per cent or more Painful congestion of the liver may likewise be benefited Venesection may be employed in all patients with intractable heart failure but under such circumstances lasting benefit is rarely produced Ordinarily the amount of blood removed should be 300 to 500 ml for an adult patient of average size without anemia

Oxygen Administration of oxygen is indicated (1) in any patient with evidence of outspoken arterial hypoxia (2) when dyspnea is severe and possibly (3) in patients with intractable congestive failure When oxygen is needed for several days

a tent is the most useful method of administration for periods of a few hours a mask is convenient effective and relatively inexpensive (Chap 273)

Thoracentesis This is a valuable procedure in many patients with congestive failure It should be employed in all severely dyspneic patients who present evidence of hydrothorax which is frequently bilateral but often confined to the right pleural cavity *Abdominal paracentesis* is indicated whenever ascites is prominent and fails to respond promptly to sodium restriction and diuretics Massive hydropericardium is a rare complication but is of great practical importance and usually calls for paracentesis

Puncture of the Legs In some patients who respond poorly to diuretic measures edema may be overcome by puncturing the skin of each leg 10 or more times with an 18 gauge needle The patient should then remain in the sitting position for 12 hr or more and should be given appropriate antibiotics usually penicillin to prevent infection

Radioiodine Depression of the thyroid gland by the administration of radioiodine is sometimes of value in patients with intractable heart failure Such administration should be carried out only by someone with extensive experience in the use of radioisotopes The subsequent myxedema which may develop in about 3 months is likely to be sensitive to desiccated thyroid in unusually small doses even as little as 4 to 8 mg daily

Special Problems in the Management of Heart Failure *Pregnancy* The physiologic adjustments that normally take place during pregnancy the increase in heart rate cardiac output and blood volume place a burden on the cardiovascular system that reaches its peak at about the seventh or eighth month of pregnancy Thereafter these functions decline and tend to approach normality up to the time of labor This hyperkinetic state of the circulation acts to diminish the cardiac reserve a reduction of which is well tolerated by the pregnant woman with the normal heart but is tolerated with varying degrees of success by the woman with organic heart disease depending on the extent to which her cardiac reserve has already been diminished by the structural lesion of the heart *The greatest danger of congestive failure to the woman with heart disease occurs at the seventh or eighth month of pregnancy*

The increase in blood flow through the heart is frequently responsible for the appearance in normal persons of functional systolic murmurs which with the edema of the ankles that is also not uncommon and the displacement of the cardiac impulse by the elevated diaphragm and the resulting mistaken impression that there is cardiac enlargement sometimes may give rise to the erroneous idea that heart disease is present The increased blood flow also tends to accentuate murmurs in those who do have organic heart disease thus occasionally revealing for the first time a hitherto undetected lesion such as mitral stenosis Though there is no diminution in vital capacity ventilation increases and the respiratory reserve is curtailed thus facilitating the appearance of dyspnea with any given effort

The chief practical problems presented by pregnancy in relation to heart disease are as follows (1) Should the woman with cardiac disease become pregnant? (2) What should be done about a woman already pregnant who presents evidence of cardiac disease? In general these questions are answered by an assessment of the patient s functional capacity and this in turn is best determined by estimation of the symptoms caused by varying degrees of activity The patient who is asymptomatic or whose dyspnea is minimal even with strenuous exertion can undertake pregnancy with practically no more risk than can the woman with a normal heart On the other hand the presence of relatively severe symptoms with ordinary activity a history of hemoptysis (indicating the probability of an already significantly elevated left auricular and mean pulmonary capillary pressure) or a previous history of congestive failure make it inadvisable that pregnancy be undertaken and may indicate that the pregnancy should be terminated The same advice should be given if auricular fibrillation is present not because of the deleterious effects of the abnormal rhythm but rather because its presence indicates that an advanced stage of rheumatic heart disease is already present Nevertheless even auricular fibrillation is not an absolute contraindication to pregnancy or its continuation to term provided the functional capacity of the heart is deemed to be reasonably good the desire for the child great and the risks understood by the parents It is the intermediate group of patients those with symptoms on moderate activity who present the most difficult problem the decision depending on a multitude of factors aside from the status of the heart the number of children in the family the economic circumstances the opportunity for restriction of activity the likelihood that the patient will cooperate in reducing the preventable stresses on the heart the willingness to accept a calculated risk etc

Since the patient with heart disease starts out with the handicap of a diminished cardiac reserve which is still further lessened by the normal physiologic adjustments of pregnancy all other stresses that confer additional burdens on the heart and circulation require meticulous attention avoidance of overexertion and emotional tension correction

of anemia careful supervision of even minor in fections correction of obesity restriction of salt intake prompt treatment of abnormal rhythms especially tachycardias and frequent search by the physician for early signs of pulmonary con gestion

TERMINATION OF PREGNANCY If the patient is already pregnant and falls into one of the unfavora ble categories or if manifestations of congestive failure appear early termination by the vaginal route should be carried out during the first trimester After this time disposition of the patient is a matter of judgment and always entails uncertainty and risk If the symptoms are mild or moderate the patient may with careful medical supervision be carried beyond the critical seventh or eighth month after which the danger diminishes On the other hand if the symptoms are severe termination of the pregnancy may be considered imperative the method being left to the obstetrician

Once the patient has arrived at term the route of delivery should be decided by the obstetrician on obstetrical grounds Usually spontaneous de livery aided by low forceps is preferable Resort to cesarean section as a routine measure is no longer considered desirable this mode of delivery being reserved only for women who are expected to face a difficult and exhausting labor

The above comments are applicable in a general way to all women with heart disease but they refer particularly to women with rheumatic heart disease and mitral stenosis since they constitute the bulk of those with heart disease in pregnancy Mitral commissurotomy has been successfully employed in some women in whom threatening symptoms have appeared during pregnancy It is generally believed however that medical supervision alone or termination of the pregnancy is preferable opera tive dilatation of the valve being reserved for a later time when the patient is not pregnant Usually pregnancy in the patient with acyanotic congenital heart disease is well tolerated Repair of coarctation of the aorta should be done prior to pregnancy The occasional development of dissecting aneurysm during pregnancy or of a cerebral vascular accident during delivery makes this condition somewhat more hazardous than other asymptomatic cardiac disorders Advice regarding future pregnancies will depend on the course of the preceding ones and on the state of the heart at the time the next preg nancy is contemplated

Intractable Heart Failure From time to time physicians encounter patients with cardiac failure who either do not show a satisfactory initial re sponse to therapy or who having previously re sponded well become progressively more refractory to management Under these circumstances the physician will do well to ask himself the following questions (1) Is the therapy adequate? (2) Is there in this patient an unrecognized etiologic factor which might be treated successfully? (3) Is some complication making the patient respond so poorly? (4) Is the intractable heart failure due to extreme myocardial impairment? These questions will now be considered in some detail

1 *Has the patient received adequate therapy for congestive heart failure*? Is the dose of digitalis properly adjusted? If the patient has been receiving a maintenance dose of less than 0 1 Gm of the powdered leaf or 0 1 mg digitoxin, there is a defi nite possibility that he has escaped digitalization because the combined effects of excretion and de struction of the drug have exceeded the daily maintenance dose Under these circumstances it is frequently desirable to administer for a few days one of the intermediate preparations such as gitalin or digoxin in a dose equal to two or three times the average maintenance of such a preparation (see p 1311 and Table 114 p 1312)

Digitalis intoxication is likewise a common cause of what may appear to be intractable heart failure The presence of undoubted signs of such intoxica tion in an individual who has been receiving a relatively small maintenance dose makes it highly probable that potassium deficit has occurred as the result of anorexia and the frequent administra tion of mercurial diuretics Under such circum stances rapid improvement may follow the adminis tration of potassium chloride 3 to 6 Gm daily in divided doses for a few days If the maintenance dose of digitalis has been relatively large then the patient may be suffering from digitalis intoxication even though there is no potassium deficit Careful inquiry should be made concerning the presence of anorexia nausea and arrhythmias due to digi talis and the less frequent and less obvious mani festations of digitalis intoxication such as blurring of vision and xanthopsia should be sought If the patient has been receiving one of the intermediate drugs the manifestations of digitalis intoxication will disappear within 3 to 6 days after withholding it If powdered leaf or digitoxin has been employed improvement may be delayed for as long as 1 to 2 weeks after discontinuing digitalis

Defective restriction of sodium is another com mon cause of apparent intractability A patient may religiously refrain from adding salt at the table or during cooking and yet fail to realize that the bread he eats and the water he drinks may be excessively rich in sodium The physician should be familiar with the sodium content of the tap water in his community and should prescribe dis tilled water whenever necessary Sodium free bread is now available at most large grocery stores

One of the commonest causes of refractory heart failure is the presence of an electrolyte disturbance These disorders have been considered above

2 *Is there an unrecognized etiologic factor which might be successfully treated?* One thinks first of all of masked thyrotoxicosis This condition may present none of its usual clinical manifestations when occurring in an elderly patient with congestive heart failure One should entertain a high degree of suspicion toward such physical signs as unusual softness of the skin excessive sweating frequent bowel movements heat intolerance unexplained tachycardia etc Even with a high index of clinical suspicion patients with thyrotoxicosis will be overlooked unless one makes it a rule to determine the protein bound iodine of the serum in all patients with congestive failure

Chronic arterial hypoxia due to primary disorders of the lung is frequently complicated by congestive heart failure and may be strikingly benefited by oxygen therapy properly administered Anemia of clinically significant degree is usually obvious upon inspection of the patient s skin and mucous membranes but it may be overlooked The possibility of thiamine deficiency due to the long standing anorexia induced by abdominal congestion should be considered in every patient with congestive heart failure The suspicion should be particularly strong when treating elderly males who live alone or individuals who partake freely of alcohol In the younger group of patients with valvular disease the possibility that smoldering rheumatic myocarditis or bacterial endocarditis is present should be kept constantly in mind

It is perhaps even more important to look for evidences of those types of cardiac disease which are particularly amenable to surgical management *Mitral stenosis may be readily overlooked in a* middle aged or elderly patient with auricular fibrillation The presence of obvious congestive failure may keep the physician from a careful search for such congenital disorders as coarctation of the aorta and patent ductus with a systolic murmur only Constrictive pericarditis is especially likely to be missed unless careful precordial palpation and fluoroscopic examination are carried out on every patient with congestive heart failure

3 *Is there a hitherto unsuspected complication?* In patients who have been subjected to repeated mercurial diuretics plus a long standing low salt diet and more particularly if anorexia has been an important symptom one should be on constant watch for those electrolyte disturbances already discussed They are likely to manifest themselves by the relatively rapid onset of refractoriness to mercurial diuretics and by the simultaneous appearance of marked lassitude and apathy The recognition of hypochloremic alkalosis of potassium deficit of sodium depletion of the salt depletion syndrome or a combination of these disorders should be made according to the criteria described above In the absence of some serious primary disease of the kidney or of some obvious grave intercurrent disorder the presence of refractoriness to mercurial diuretics constitutes strong evidence for the presence of one of these electrolyte disturbances

Advanced renal disease frequently is present in patients with congestive failure and especially in those who have either hypertension or bacterial endocarditis During the initial phase of management the manifestations of congestive failure may overshadow those of the less obvious but often more serious renal disease The coexistence of nitrogen retention and of a urine of low specific gravity despite a small urine volume makes it highly probable that there is grave functional impairment of the kidneys and that the management of the cardiac failure and more particularly of electrolyte disturbances will be relatively unsuccessful

Pulmonary infarction discussed in Chap 236 is one of the commonest causes of intractable heart failure If this complication is recognized and vigorously treated either with anticoagulants or in suitable cases by venous ligation the heart may again respond to treatment after a period of days or weeks has elapsed In many instances the expected manifestations (pleural pain hemoptysis and changes in the x ray) will be absent and the sole clues to pulmonary infarction may be unexplained elevations of temperature leukocyte count or sedimentation rate plus aggravation of the cardiac status and at times an evanescent increase *in the serum bilirubin values*

4 *Is the intractable heart failure due to extreme myocardial impairment?* This suspicion should be entertained seriously only after the problem has been approached from the standpoint of the questions above Once one is satisfied that the therapy is entirely adequate that there is no complicating unrecognized etiologic factor and no serious complication one is justified in entertaining the question of myocardial disease so advanced that the heart failure has become and will remain intractable Under such conditions the patient has little to lose by receiving radioactive iodine and he may receive some benefit from it

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B DISEASES OF THE VASCULAR SYSTEM

227 HYPERTENSIVE VASCULAR DISEASE

John P Merrill

Arterial hypertension in man may be arbitrarily divided into two categories pulmonary hypertension and systemic hypertension (Table 115) The more important problems related to pulmonary hypertension have been considered in Chap 224

Systemic hypertension is the manifestation of an abnormal state of the circulation just as fever is a sign of altered temperature regulation The word *hypertension* in itself implies nothing as to the associated prognosis or organic vascular or renal disease Indeed the role of elevated blood pressure in the production of aggravation of vascular disease is a disputed but important association which will be discussed separately As a clinical phenomenon hypertension may be diagnosed if on repeated examinations the blood pressure is found to be above that considered normal for adolescents of similar racial and environmental background In North American adults 140/90 may be regarded as abnormally high arterial pressure for coolies in Peiping 125/80 might have a similar significance

It is now apparent that the hypertensive syndrome has no single clear cut etiology Many factors are involved some of which may be thought of as mere exaggerations of the physiologic mechanisms by which normal arterial pressure is maintained Others are obviously abnormal in the sense that they play little or no role in normal circulatory regulation and are prominent only in disease states Any or all of these factors may be involved in any given case of hypertension It is not surprising therefore that in spite of a vast amount of interest and work no single therapeutic agent for the treatment of hypertension has come to light The physician or student who undertakes to study or treat hypertension must seek to understand the various mechanisms which may be involved when he attempts to evaluate their importance in the individual problem

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Advanced renal disease frequently is present in patients with congestive failure and especially in those who have either hypertension or bacterial endocarditis During the initial phase of management the manifestations of congestive failure may overshadow those of the less obvious but often more serious renal disease The coexistence of nitrogen retention and of a urine of low specific gravity despite a small urine volume makes it highly probable that there is grave functional impairment of the kidneys and that the management of the cardiac failure and more particularly of electrolyte disturbances will be relatively unsuccessful

Pulmonary infarction discussed in Chap 206 is one of the commonest causes of intractable heart failure If this complication is recognized and vigorously treated either with anticoagulants or in suitable cases by venous ligation the heart may again respond to treatment after a period of days or weeks has elapsed In many instances the expected manifestations (pleural pain hemoptysis and changes in the x ray) will be absent and the sole clues to pulmonary infarction may be unexplained elevations of temperature leukocyte count or sedimentation rate plus aggravation of the cardiac status and at times an evanescent increase in the serum bilirubin values

4 *Is the intractable heart failure due to extreme myocardial impairment?* This suspicion should be entertained seriously only after the problem has been approached from the standpoint of the questions above Once one is satisfied that the therapy is entirely adequate that there is no complicating unrecognized etiologic factor and no serious complication one is justified in entertaining the question of myocardial disease so advanced that the heart failure has become and will remain intractable Under such conditions the patient has little to lose by receiving radioactive iodine and he may receive some benefit from it

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particularly in the elderly arteriosclerotic patient Here failure of the rigid vessel wall to distend with the systolic thrust of the heart results in a sudden increase in pressure in the system producing a high systolic pressure Similarly lack of elastic "recoil results in a rapid drop of pressure in diastole and this failure to maintain the resting pressure in the vascular bed may be recorded as a low diastolic pressure

4 An increase in *cardiac output* such as is mediated through exercise fever or thyrotoxicosis may cause increases in blood pressure by increasing the amount of blood pumped into the vascular system per unit of time Since the effect is primarily a result of the ventricular contraction the predominant effect upon blood pressure is an increase of the systolic phase As a clinical phenomenon this has much less significance for the hypertensive syndrome than does elevation of the diastolic blood pressure Decrease in cardiac output secondary to severe myocardial damage results in hypotension If compensatory vasoconstriction occurs the diastolic pressure may be relatively well maintained and the hypotension is characterized by a low systolic and a narrow pulse pressure

5 The single most important factor in the production of the type of arterial hypertension with which the physician is usually concerned is an *increase in peripheral resistance* The greatest part of this increase is contributed by the arteriolar segments Relatively small changes in caliber cause marked changes in resistance which varies inversely as the fourth power of the radius of the lumen Thus a decrease of 10 per cent in the average arteriolar lumen will lead to a rise of 30 per cent in mean arteriolar resistance The diastolic pressure which represents the residual resistance in the peripheral vascular bed after systole more closely reflects the factor of peripheral resistance As reflecting this factor elevation of the diastolic pressure is of crucial importance in the syndrome concerned in a study of hypertension in man though systolic hypertension alone which may result from several causes of increased stroke volume may have little bearing in itself *Decrease* in arteriolar tone secondary to toxins nervous influence or drugs results in increase in caliber and may produce *hypotension*

Alterations in blood pressure in either direction produced by changes in any of the five factors previously mentioned are modified by reflex arcs of the autonomic nervous system Through vasoconstrictor or vasodilator fibers these arcs change arteriolar tone and lumen following appropriate stimulation of receptors on the afferent side of the arc Similar reflex arcs modify the cardiac output Medullary centers exist for control of cardiac rate as well as for vasoconstrictor and vasodilator effects These medullary centers in turn may be influenced by higher vasomotor centers situated in the hypothalamus and possibly even in the cerebral cortex Stimulation of vagal afferent fibers located in the aortic arch and the heart may result in alteration in caliber of the blood vessels through impulses transmitted via these vasomotor centers over efferent fibers to the vasculature A rise in blood pressure by stretching special proprioceptors in the aortic wall is thought to be the stimulus for the resultant depressor response Similar receptors are located in the carotid sinus Stimulation of these by increase in pressure may lead to vasodilator responses whereas decrease in pressure may produce a vasoconstrictor reflex through the afferent limb of the reflex arc The sinus and aortic nerves are the so called buffer nerves" and together make up an important mechanism for controlling arterial blood pressure The rise in diastolic pressure which occurs when the upright position is assumed is one of the many important manifestations of this control

INCREASES IN BLOOD PRESSURE SECONDARY TO CHANGES IN ARTERIOLAR CALIBER

From the foregoing it would appear that factors which influence arteriolar tone and caliber play an important role both in maintaining normal blood pressure and in producing hypertension The following factors have been thought to be of importance in influencing arteriolar tone

Decrease in Vasodilator Tone Some authorities hold that the kidney elaborates a vasodilator substance whose production is impaired in renal disease or nephrectomy Practical applications of this theory are lacking in the clinical hypertensive syndrome

Humoral Agents Which Raise Smooth Muscle Tone For more than half a century workers in the field of hypertension have been interested in circulating humoral substances whose primary action is to increase arterial tone Some of these substances have been thought to arise in the central nervous system but the greatest interest has centered around the release by a kidney whose blood supply has been compromised (though not made anoxic) of a substance (renin) which by interaction with a serum globulin is capable of causing an increase in smooth muscle tone in arterioles The resultant pressor substances (angiotonin hypertensin) have been investigated and in some cases antiserums to renin have been prepared which will prevent its action in animals Among the many other substances found in the circulating plasma of hypertensive animals causing pressor responses are serotonin and pherentasin Investigators have isolated from dogs a pressor substance released from the central nervous system on centripetal vagal stimulation

Table 115 CLASSIFICATION OF HYPERTENSION

I Pulmonary hypertension
II Systemic hypertension
- A Systolic hypertension only
  - 1 Increased stroke volume
    - *a* Thyrotoxicosis
    - *b* Anemia
    - *c* Heart block
    - *d* Arteriovenous fistula
    - *e* Psychogenic
  - 2 Rigidity of the aorta
    - *a* Arteriosclerosis
- *B* Combined systolic and diastolic hypertension *
  - 1 Renal
    - *a* Pyelonephritis
    - *b* Glomerulonephritis
    - *c* Congenital lesions
    - *d* Obstructive lesions
    - *e* Renal vascular occlusion
  - 2 Endocrine
    - *a* Acromegaly
    - *b* Adrenal cortical hyperfunction
    - *c* Pheochromocytoma
  - 3 Neurogenic
    - *a* Brain tumor (rapidly expanding)
    - *b* Cerebrovascular accidents
    - *c* Diencephalic syndrome
    - *d* Poliomyelitis
    - *e* Psychogenic
  - 4 Unknown etiology
    - *a* Essential hypertension (benign)
    - *b* Eclampsia
  - 5 Miscellaneous
    - *a* Coarctation of the aorta
    - *b* Increased intravascular volume

* Any of the conditions associated with diastolic hypertension may become rapidly progressive (malignant) This occurs much more frequently in the so called essential hypertension

occurs in a series of elastic tubes The larger tubes represented by the arteries gradually decrease in caliber through the arterioles to the capillaries and similarly decrease the magnitude of each pulsation until in the capillaries the flow becomes steady In this system the pulsating force is provided by the contraction of the left ventricle the elasticity by the walls of the arteries and the major portion of the resistance to flow by the arteriolar bed The pressure produced at the peak of ventricular contraction in this elastic system is represented by the systolic blood pressure and the total resting resistance of the system in ventricular diastole by the diastolic pressure The difference between these two values is the pulse pressure The mean arterial pressure is usually thought of as one half the sum of the systolic and diastolic pressures However the true mean pressure which is the average pressure throughout the cardiac cycle is not faithfully reflected by this value since the fall in pressure from the systolic to the diastolic level is not a decline over a steady slope In measuring the arterial blood pressure the observer is assessing a value which is determined by a number of factors not ordinarily measured directly

We may consider these factors in order

1 Since increasing resistance to flow is developed by increasing viscosity *blood viscosity* is one factor altering blood pressure Blood viscosity is influenced chiefly by the concentration of the plasma proteins and of the white and red corpuscles suspended in it Marked polycythemia may thus give rise to hypertension both by reason of increased blood viscosity and by the increased whole blood volume

2 *The amount of whole blood or plasma in the intravascular compartment* contributes also to the arterial pressure Since the intravascular fluid except for the blood proteins is continuous across the capillary walls with extracellular fluid in general the volume of this latter compartment also contributes to arterial blood pressure Thus severe depletion of either or both compartments by bleeding or acute dehydration will produce hypotension increase of the volume of either may result in hypertension Factors modifying the retention or excretion of sodium and water will affect the volume of extracellular fluid and may produce alteration in blood pressure Since several factors of the adrenal cortex are concerned with sodium retention it is to be expected that hyperfunction of the adrenal cortex may be associated with excess salt and water retention increased plasma volume and hypertension Certainly many cases of adrenal cortical hyperfunction (Cushing s syndrome) exhibit hypertension whereas untreated hypoadrenalism (Addison s disease) may be characterized by hypotension This relationship is not a consistent one however for some patients with adrenal cortical hyperfunction show no hypertension and similarly patients with cyanosis and congenital heart disease who have increased blood volumes may fail to show hypertension Possibly in the latter instance a decrease in cardiac output may account for this as it certainly does in patients who with the development of heart failure show an increase in blood volume but a fall in cardiac output Thus modification of one of the five factors by another or all of the others may influence the alteration in blood pressure

3 In a sense *the rebound of the elastic arterial walls in ventricular diastole* serves to maintain the propelling force of the blood in the interval between systolic contractions It thus serves together with the peripheral resistance to flow in the arteriolar bed to maintain the resting or diastolic pressure in the vascular system The effect of decreasing elasticity of the large vessel walls may be seen

likely to be correlated with longevity In more than a third of the population however arterial hypertension as manifested by resting blood pressures of 150/90 or above may be noted as a transient phenomenon in early adult life and is the usual finding beyond the age of sixty Although in themselves such increases in blood pressure may be of little significance in any one individual statistics based on hundreds of thousands can leave no doubt that even occasional rises in resting levels of pulse and blood pressure are associated with a shortening of the life span

Factors of importance in alterations of arterial blood pressure may also be found in a consideration of race environment individual heritage and the state of activity Thus hypertension occurs earlier and in a higher percentage of Negroes both in the United States and in tropical Panama than in white or Indian populations Women develop hypertension slightly more frequently than men but appear to tolerate it better The basal pressures determined on awakening before morning activity begins are lower than during the day 90/60 in many healthy whites and 80/50 or less in many natives of the tropics and of Asia Sitting or standing normally raises the diastolic levels 5 to 10 mm Hg exercise and hypoxia or marked anemia lower the diastolic and raise the systolic level

Recent statistical studies indicate that although blood pressure tends to rise with age in the relatives of both hypertensives and nonhypertensives blood pressure elevations are found earlier in the relatives of the hypertensive population and tend to remain higher throughout their life span Similarly hypertension frequently develops earlier and with greater severity in successive generations with hypertensive predecessors In those with the hypertensive predisposition inherited or not a rise in systolic and diastolic pressures may be caused by chilling anger frustration anxiety or even pleasant anticipation of an exciting event whereas others with no predisposition may show no rise even with the most intense emotional stimuli The value obtained with the sphygmomanometer is thus only one of the many factors whose importance must be assessed in considering the significance of alterations in blood pressure

CLASSIFICATION OF HYPERTENSION

A system of classification of hypertension is presented in Table 116 It should be noted that systemic hypertension may be differentiated by reason of the phase in which the elevation occurs Marked elevation of systolic pressure with little or no elevation of diastolic pressure has a different etiologic connotation and even more important an entirely different prognostic significance than does elevation of the diastolic phase As has been pointed out previously predominance of systolic elevation depends more upon the factor of cardiac output Predominance of diastolic elevation is a manifestation of increased residual resistance in the peripheral vascular bed after systole and as such more closely represents the clinically significant abnormality in the hypertensive syndrome The term *essential hypertension* has been employed to indicate those cases of hypertension for which a specific endocrine or renal basis cannot be found and in which the neural element may be only a mediator of other influences Since even this latter relationship is not entirely clear it is more properly listed for the moment in the category of unknown etiology The term *essential hypertension* defines simply by failing to define hence it is of limited use except as an expression of our inability to understand adequately the forces at work Nevertheless the bulk of patients with significant and persistent elevation of diastolic pressure form a fairly uniform group for which no well defined etiologic process has been delineated From the standpoint of wide acceptance the term probably should be retained Unquestionably cases of essential hypertension in the progressive form may develop a renal component which perpetuates this syndrome as a result of development of vascular lesions in the kidney The development of vascular lesions here and elsewhere has served for some authors to differentiate *hypertensive disease* from *hypertension* which latter term connotes only elevation of blood pressure without associated vascular lesions The prognostic significance of this division is obvious but the dividing line is often difficult to draw Essential hypertension may be further subdivided into two types *benign* and *malignant* These terms should be employed only as relating to the rapidity and severity of the vascular disease accompanying increased blood pressure levels The malignant type may be superimposed upon the benign type occasionally however it may be so rapid in onset and so severe in its course as to appear a separate entity In addition the severity and rapid progress of vascular disease associated with hypertension primarily renal in

Table 116 CURABLE HYPERTENSION

Systolic hypertension only	*Combined systolic and diastolic hypertension*
Thyrotoxicosis	Brain tumor
Arteriovenous fistula	Unilateral renal disease
Anemia	Adrenal cortical hyperfunction
	Pheochromocytoma
	Pituitary tumors
	Coarctation of the aorta
	Increased intravascular volume
	Eclampsia
	Polycythemia

which has common properties with serotonin and has been postulated as an explanation for the failure of so called neurogenic hypertension to respond to sympathectomy To the great misfortune of the hypertensive population the role of all these substances in chronic hypertension in man is still obscure The hormones of the adrenal medulla however are humoral agents which can and do play a well defined role in some instances of human hypertension Primarily implicated are epinephrine and its demethylated analogue norepinephrine From the physiologic viewpoint norepinephrine appears more closely associated with the human hypertensive syndrome Its action is characterized by an increase in peripheral resistance (primarily because of increased small vessel tone) with no increase or an actual fall in cardiac output Functioning tumors of the adrenal medulla and chromaffin tissue elsewhere can closely mimic the clinical picture of hypertensive disease although in essential hypertension blood levels of norepinephrine are not elevated

Humoral Agents Which Potentiate either Neurotonic or Humoral Tonic Effects It has been suggested that the kidney may be the site of a vaso exciter material (VEM) which potentiates (in the experimental animal) the response of small arterioles to topical application of epinephrine Of much greater significance however is recent evidence both in the experimental animal and in human beings that the kidney s role in renal hypertension may be its failure to excrete or to metabolize a circulating pressor substance similar to or identical with norepinephrine With the exception of Cushing s syndrome the role of the adrenal cortical steroids in producing the usual varieties of hypertensive disease is still obscure We can only conclude from the wealth of experimental and clinical data that the adrenal cortex probably plays a role in the maintenance of hypertension much as it does in normotension

Nervous Constrictor Influence As an explanation for the increased peripheral resistance which appears to be common to the hypertensive syndrome almost independent of its etiology it is natural to inquire into the role of increased vasomotor tone Increased vasomotor tone and augmented spontaneous vasomotor activity have been observed experimentally under the microscope and are well known to occur in many hypertensive and prehypertensive patients Many factors which block or reduce sympathetic tone at high levels such as psychotherapy and sedation and sympathectomy and sympatholytic drugs at a more peripheral mechanism tend to decrease blood pressure Similarly factors known to augment constrictor nervous influence such as emotion and chilling tend to increase blood pressure Possibly in some cases the central nervous system participates by elaboration of the humoral agent It should be remembered also that the adrenal medulla is under the influence of nervous stimulation When the autonomic pathways are interrupted by chemical blockade of the sympathetic ganglions it has been found that in both normo and hypertensive patients blood pressure falls are greater when the initial blood pressure is high In both normo and hypertensive patients however elevation of the blood pressure by the administration of norepinephrine leads to a decrease in the extent of the blood pressure fall which may be obtained by ganglionic blockade In spite of the fact that vasomotor activity is not always increased in essential hypertension it is reasonable to conclude that neurogenic mechanisms play prominent contributory roles In established hypertension the vasomotor centers continue to regulate blood pressure levels in response to both pressor and depressor stimuli Thus although fixed hypertension is rare nervous influences however play a lesser role in well established or malignant hypertension because of the increased participation of humoral factors or because of decreased reactivity of the blood vessels secondary to pathologic change

CONSTITUTIONAL FACTORS IN HYPERTENSION

In attempting to assay the significance of alterations in blood pressure in the light of the various factors which have been delineated it is most important to remember that range of blood pressure compatible with normal activity and good prognosis may be extremely wide when compared with the range of such parameters as body temperature This is truer perhaps of the systolic than of the diastolic variation but it is to be emphasized that daily or even hourly fluctuations in blood pressure per se may be without real prognostic significance

In infancy arterial pressure may be 70/45 It then rises in late infancy and early childhood to values approximating 80/55 and by adolescence reaches levels of 95 to 110 systolic and 65 to 80 diastolic The upper limit arbitrarily chosen by many for the normal blood pressure in the adult is 140/90 All values cited above are approximations and fluctuations in either direction may occur without true prognostic significance Lower values are often diagnosed and treated as low blood pressure because of the well perpetuated myth that normal systolic blood pressure should equal the sum of 100 plus chronologic age Levels based on this formula however should be regarded as a statistically common misfortune rather than the ideal concomitant of advancing years In the absence of obvious causes for true hypotension values below that proposed by such a formula are in fact

mation of the hematocrit and erythrocyte count Phlebotomy the administration of phenylhydrazine hydrochloride radioactive phosphorus and irradiation have been used successfully in treatment *Pituitary tumors* accompanied by hypertension may be associated with the picture of hyperadrenalism or with that of acromegaly in which case the characteristic facies increase in head hand and foot size as well as x rays of the extremities and sella turcica may confirm the diagnosis The therapy of choice is irradiation

TOXEMIAS OF PREGNANCY

The toxemias of pregnancy are arbitrarily divided into preeclampsia and eclampsia Eclampsia is characterized by a more severe course and more diffuse lesions it differs from preeclampsia by the presence of convulsions and coma The syndrome is manifested by hypertension proteinuria and retention of fluid Common symptoms are headache visual disturbances and epigastric pain In the past the incidence of eclampsia has varied from 0 2 to 1 5 per cent With better prenatal care however this incidence has markedly decreased in recent years The disease is more common in primiparae than in multiparae though this may reflect only the decreased tendency of toxemic primiparae to become pregnant again Diabetes multiple births and hydatidiform moles are all reported as increasing the incidence of toxemias The primary pathologic lesions are seen in the kidneys and consist of thickening of the walls of the glomerular capillaries and the capillary basement membrane In the more severe cases petechial hemorrhages and small areas of necrosis are found in the brain In severe eclampsia the liver shows characteristic lesions consisting of irregular areas of hemorrhage and necrosis This may occasionally be severe enough to produce jaundice Bilateral symmetric necrosis of the cortices of the kidney occurs most often at the onset of eclampsia The etiology is still obscure Many of the reported cases of eclampsia may be simply the aggravation by the pregnant state of preexisting essential hypertension or of glomerular nephritis When these can be shown to be absent in the first 5 months of pregnancy it is postulated that a toxic or pressor substance formed in the placenta possibly at the site of placental infarction may be implicated in the production of the profuse vascular lesions

Course True eclampsia or preeclampsia rarely manifests itself before the sixth month of pregnancy In the cases which are carefully followed the earliest clues may be headache anorexia proteinuria elevations of blood pressure and excessive gain in weight There is frequently some degree of oliguria in eclampsia and in severe cases frank renal failure with anuria may supervene Marked hematuria is not usually seen except in association with cortical necrosis In the absence of frank renal failure renal blood flow is usually normal but there is characteristically a depressed filtration rate In the severe cases convulsions are characteristic and may be the cause of death Termination of pregnancy is usually accompanied by marked improvement although symptoms may continue for as long as 24 to 36 hr after delivery The recovery stage is usually characterized by a drop in blood pressure and a profuse diuresis with loss of edema The prognosis is good in carefully managed patients without severe renal lesions The internist must concern himself with the possibility of the development of permanent renal disease or hypertension following eclampsia Unfortunately there is no agreement on the frequency with which this occurs In most of the reported series some renal disease and hypertension persist following eclampsia but it is not clear whether this is due to aggravation of preexisting renal disease and hypertension or whether it dates specifically from the eclampsia Severe previous eclampsia in women over thirty five contraindicates a further pregnancy In the presence of slight hypertension or minimal urinary findings the patient may be allowed to become pregnant and carefully followed during her pregnancy with the possibility of electively terminating it when signs of eclampsia appear There is no good evidence that normal well-conducted pregnancy aggravates mild "essential" hypertension if toxemia does not supervene Patients with preexisting renal disease however may do poorly particularly if functional impairment exists

The *treatment of toxemia* should be divided into prophylactic and therapeutic measures Prophylaxis consists of careful surveillance with restriction of sodium to less than 2 Gm per day if edema appears The treatment of severe eclampsia is the termination of pregnancy Medical measures are similar to those outlined for the treatment of hypertensive encephalopathy Magnesium sulfate as well as protoveratrine has been used with good results It has been reported that the use of Apresoline in the hypertensive disease of toxemia of pregnancy is more specific than for other forms of hypertension Massive doses of penicillin which appear to exert some antitoxic action have been used with some success and good results have been reported from the prophylactic use of stilbestrol

SYSTEMIC HYPERTENSION

Signs and Symptoms The signs and symptoms of hypertension can rarely be attributed to the elevated blood pressure itself A large number of patients with elevated blood pressure may have

origin may justify the term *malignant hypertension*

Many factors involved in the hypertensive syndrome have now been delineated It may be permissible to attempt to integrate them in a theoretic case of human essential hypertension in a fashion which lays much stress upon the primary role of nervous vasoconstrictor influences In this idealized view an individual by reason of inherited traits including race and sex may be particularly susceptible to vasomotor reactions resulting from a stressful environment Specific reasons for this susceptibility might include emotional instability a labile vasomotor apparatus possibly including the vasomotor center in the medulla and a peripheral vasculature which hyperreacts to nervous constrictor stimuli Such an individual would manifest early in life greater rises in blood pressure in response to environmental stimuli than his fellow born without these genetic traits Such abnormal responses might be elicited by the cold pressor test and Valsalva maneuver During early adult life these rises would be more frequent reach higher levels and tend less and less to return to so called normal values The continued stress of pressure upon a genetically sensitive vasculature might then result in small blood vessel changes which would be manifest in the optic fundi and kidneys With the involvement of the kidneys and possibly the adrenals a second humoral mechanism might originate which could then overlay and finally completely dominate the original neurogenic origin At this point although the labile vasomotor response might still be elicited its importance from an etiologic and therapeutic standpoint would be secondary Such a formulation is admittedly speculative It does however fit many of the observed facts Although many doubt that increased pressure per se may cause vascular disease in the author s view the statistical correlation in mortality tables is too impressive to neglect By analogy too the pulmonary vascular disease that may result from prolonged increased pulmonary arterial pressure with mitral stenosis suggests very strongly that this relationship may obtain

A second and possibly more important classification has been constructed in Table 116 Such a table emphasizes the fact that the physician confronted with the problem of hypertension must think first of those situations in which the hypertension may be associated with a specific defect which may be amenable to specific therapy A causal relationship of this type may be difficult to establish and may be defined only by the resultant success or failure of therapy Nevertheless the opportunity to cure hypertension must be sought diligently in each hypertensive patient The diagnosis and treatment of *thyrotoxicosis* have been discussed in Chap 64 The presence of an *arteriovenous fistula* may be manifested by systolic hypertension and a wide pulse pressure and may be diagnosed by the presence of a murmur or thrill over the site of the abnormal communication This may be over the peripheral vessels where involved or a typical machinery murmur may be heard over the left precordium in the case of patent ductus arteriosus Both of these conditions may be amenable to surgical correction *Adrenal cortical hyperfunction* may be manifest by hypertension as well as the other signs of Cushing s syndrome (Chap 66) Osteoporosis hirsutism buffalo hump " striae and disorders of glucose metabolism are typical *Pheochromocytoma* though rare produces a completely curable form of hypertension when surgery is performed before the vascular disease has become irreversible In spite of such diagnostic techniques as perirenal air injection and retroperitoneal insufflations with oxygen the newer pharmacologic agents for provocative and blocking tests and the assay of urinary pressor amines the diagnosis remains extremely difficult and may be established only by exploration Pheochromocytoma in addition to the typical intermittent attacks may produce a steady hypertension The problem is discussed further in Chap 67 The diagnosis of *coarctation of the aorta* if considered will usually be made by comparison of blood pressure in the arm and leg and appropriate x rays of the chest may show the typical notching of the ribs *Unilateral renal disease* remains a problem Even when unilateral renal disease can be demonstrated in conjunction with hypertension involvement of the other kidney by vascular damage may militate against cure by nephrectomy Similarly a strong family background of hypertension may make the coexistence coincident rather than causal Occlusion of a renal artery or one of its branches should be suspected when malignant hypertension appears suddenly in patients with no previous history In suitable cases cures may be effected by nephrectomy or by the placing of arterial grafts Translumbar aortography may be the sole way to make this diagnosis since little impairment in over all renal function may be evident Where unilateral renal disease is suspected as a cause for hypertension careful functional studies of both kidneys should be made If such studies reveal no trace of disease in one kidney and marked involvement in the other removal of the diseased organ may be expected to produce significantly prolonged lowering of the blood pressure in about 50 per cent of the operated patients In the author s view the stress should be placed upon the presence of one completely normal kidney rather than total lack of function in the other since by the time this latter condition is evident both kidneys may well be involved *Polycythemia* as a cause of increased intravascular volume may be diagnosed upon esti

racial origins known to be susceptible to hypertensive disease with high relatively fixed diastolic pressures are apt to do badly On the other hand women apparently tolerate elevated blood pressure and even hypertensive vascular diseases better than do men Every physician interested in hypertensive disease has followed women and an occasional man through many years of relatively good health with persistent diastolic pressures of 120 mm or more The degree of retinopathy may give some clue as to the prognosis although this in general is a better guide to the progress than to the ultimate prognosis since even severe retinopathy may be reversed occasionally by appropriate therapy and rarely improves spontaneously Papilledema and renal insufficiency are extremely grave prognostic signs in every instance The occurrence in the hypertensive patient of myocardial infarction congestive heart failure or cerebral vascular accident signifies a poor prognosis although again every hypertensive clinic has its share of patients constituting exceptions to this general rule Emotional instability while making the treatment somewhat more difficult does not otherwise affect prognosis itself Poor response to adequate treatment of any sort including failure to correct obesity frequently indicates impaired prognosis

Diagnosis The diagnosis of hypertension may be made with a blood pressure cuff and the diagnosis of hypertensive vascular disease by the usual methods for evaluating the cardiovascular system kidneys and optic fundi The differential diagnosis should from the very first include disease states giving rise to hypertension for which more specific therapy exists A list of these which should be considered during the first evaluation of any hypertensive problem is given in Table 116

Table 117 FACTORS INDICATING AN ADVERSE PROGNOSIS IN HYPERTENSION

- Negro origin
- Youth and male sex
- Persistent diastolic pressure > 110
- Marked cardiac enlargement
- EKG changes of ischemia or left ventricular strain
- Renal functional impairment
- Retinal hemorrhages and exudates
- Angina pectoris
- Myocardial infarction
- Cerebrovascular accident
- Congestive heart failure
- Marked retinal arteriolar sclerosis
- Nitrogen retention *
- Papilledema

* Nitrogen retention when due to vascular disease of the kidney indicates a very grave prognosis Its occurrence in primary renal disease with only mild hypertension may be less important

Treatment

Principles of Therapy Whatever the form of therapy selected it must not be forgotten that the physician who treats hypertension is treating the patient as a whole rather than the separate manifestations of a disease The first principle of the therapy of hypertension is the knowledge of when to treat and when not to treat Two essentially opposing viewpoints are maintained in this regard with various shades of opinion in between Both agree that the accelerated phase of hypertension with a high diastolic pressure and rapid progress of vascular lesions in the retinas heart and kidneys markedly affects the prognosis and justifies any form of treatment aimed at lowering the blood pressure except in the presence of marked nitrogen retention The differences are sketched in Table 118

The viewpoint indicated on the right in Table 118 is espoused by the author and henceforth the discussion of therapy will be oriented from this point of view

Selection of Patients for Therapy In the decision to institute treatment the factors delineated in the paragraph on prognosis must bear considerable weight Factors of increasing gravity shown in Table 117 are increasingly important indications for specific therapy Frank nitrogen retention however may contraindicate and obviate any specific form of depressor therapy Sudden marked and persistent elevation of diastolic pressure may precede signs and symptoms and as such indicate need for therapy A knowledge of when to withhold specific treatment is equally important A woman who has tolerated her diastolic pressure of 120 for 10 years without symptoms or deterioration does not need immediate specific treatment for hypertension Marked elevation of systolic pressure with little or no rise in diastolic does not constitute an indication for depressor therapy This is particularly true in the elderly or arteriosclerotic patient even though the diastolic pressure may also be moderately elevated A trial of mild forms of therapy including psychotherapy reducing diets sedation or mild depressor agents which fails to improve signs or symptoms may justify more intensive forms of therapy The physician must however carefully weigh the value of making his patient blood pressure conscious by a specific regimen and regular follow up against real need for any particular form of therapy Above all in treatment or prognostication he must avoid engendering in the patient a fear of the disease which may be unwarranted in our present state of knowledge Promising therapies are available however and it should be remembered that the forms of treatment are not mutually exclusive Particularly it should

no symptoms or signs whatever In the more advanced stages of hypertensive disease signs and symptoms depend upon the organ involved by the vascular disease accompanying the hypertensive process These include of course cerebral arterial and arteriolar disease coronary artery disease congestive heart failure and renal failure which will be discussed in separate chapters A not infrequent early symptom is the presence of headache This may take any form but classically is a dull pounding occipital headache which is present upon awakening in the morning and tends to wear off during the day Many patients with hypertension complain of nonspecific difficulties such as weakness nervousness flatulence palpitation and dizziness Since hypertensive patients are prone to emotional and psychic difficulties it is frequently difficult to evaluate these symptoms

Epistaxis may occur as well as microscopic and even gross intermittent hematuria accompanied by moderate proteinuria The latter findings may signify vascular involvement of the kidney but should alert the physician to the possibility of preexisting renal disease An important physical finding which may give some clue to the prognosis and progress of the vascular disease is the change in the optic fundi Early changes may include diminution in caliber of the smaller vessels most distant from the disk Tortuosity of the larger vessels close to the disk occurs in hypertensive disease but may also be seen in arteriosclerosis without hypertension and is of little significance to the hypertensive process itself Nicking of the veins by the arterioles with marked variation in the arteriolar caliber is a pathognomonic sign An increased light reflex signifies thickening of the vessel wall With advancing changes small flame shaped hemorrhages and glistening white exudates may make their appearance A serious prognostic sign indicative of advanced disease is papilledema manifested by blurring of the disk margins This should be particularly evaluated at the temporal margin since some degree of blurring of the nasal margin may be physiologic Separation of the retina has been observed in the acute hypertensive episodes of eclampsia Although somewhat unusual there may be marked differences in the degree of involvement of the retinas The visual symptoms usually depend upon the degree of involvement and the location of the lesions

Patients with hypertensive disease occasionally suffer from acute episodes characterized by marked rise in blood pressure above the previous level and by disorders of the nervous system which last for minutes hours or days and then disappear without clinical evidence of lasting damage Such episodes described as *hypertensive encephalopathy* are not limited to any single etiologic type of hypertensive disease but are particularly common in association with renal disease especially where a common factor such as acute glomerulonephritis or disseminated lupus erythematosus has produced both vascular lesions and hypertension Spasm of cerebral vessels is generally thought to be the cause of these attacks although adequate demonstration of this has yet to be made Small thrombi and edema play a role in some cases This syndrome may frequently simulate the hypertensive crises of pheochromocytoma or mimic brain tumor The clinical syndrome appears in two forms depending upon whether the disturbances in the nervous system are chiefly of generalized or of focal nature

The general form usually appears in individuals without previous long standing hypertension It may occur in women with eclampsia and in children and young adults with acute glomerulonephritis Rapidly progressing malignant hypertension is frequently accompanied by hypertensive encephalopathy Aside from a rapidly rising blood pressure the attacks are characterized by headache visual disturbances which may progress to blindness papilledema vomiting stupor coma stertorous breathing psychoses and convulsions All of these manifestations may be hastened and enhanced by the administration of excessive amounts of fluid

The focal type of hypertensive encephalopathy may appear in any individual with chronic hypertension but is especially frequent in older individuals and in the malignant form of the disease Loss of consciousness convulsions and paralysis involving one half of the body are especially common and the clinical picture though reversible may exactly resemble cerebral vascular accident due to hemorrhage thrombosis or embolism at the beginning The differentiation may be impossible until the patient has been observed for a number of hours or even for several days

Prognosis in Hypertension Few problems in clinical medicine are as difficult or as controversial as the evaluation of the prognosis for any individual patient with early but marked hypertension Although the statistics of the insurance companies give us a clear picture of the trend individual variation in tolerance to hypertension and hypertensive disease is marked A few of the factors affecting prognosis have already been mentioned In Table 117 are listed factors which are known to affect adversely the prognosis in patients with hypertension These are listed in order of increasing gravity Systems of classification of hypertension characterizing the disease in varying grades of severity and with varying prognoses have been devised on the basis of (1) retinal changes and (2) a combination of the factors listed in Table 117 plus PSP excretion and response to sedation It can be concluded that young male patients of

an emotionally labile patient with numerous emotional problems and psychosomatic complaints cannot always be told—because of the absence of vascular or renal disease—simply to forget his problems In the vast majority of instances a discussion of the problem with reassurances fortified by mild medication and follow up visits at infrequent but regular intervals will do more good

Dietary Management Obesity is frequently a sign as well as a complication of the hypertensive personality Since it has an undoubted adverse effect upon prognosis and progress of the disease it should be specifically treated by an adequate weight reducing regime such as has been outlined in Chap 21 The patient should fully understand the necessity for this regime without being frightened by it

There can be no question but that in the hands of certain workers diets low in sodium and in protein have resulted in striking amelioration of hypertensive vascular disease Of these the so called rice diet " containing 200 mg of sodium 25 Gm of protein and approximately 2000 nonprotein calories is an example Recent work has indicated that it is the low sodium content rather than the protein deficiency that is responsible for the beneficial results The true rice diet probably does not maintain nitrogen balance and it must be strictly adhered to for at least 6 to 8 weeks during which time most patients find it extremely unpalatable More palatable diets may be planned which contain less than 600 mg of sodium chloride per 24 hr and among several excellent booklets on this subject one is prepared for the patient by the American Heart Association For the treatment of hypertension per se 0 5 Gm of sodium chloride constitutes a maximal dietary salt intake although congestive heart failure and edema per se may respond at slightly higher levels Cation exchange resins which prevent absorption of dietary sodium have been used with success to effect decreased sodium absorption from diets containing more than 1 Gm of ingested sodium chloride and mercurial diuretics are an additional adjunct Such programs may make meals more palatable for many patients particularly with the judicious use of one of the salt substitutes The usual precautions should be observed with the ingestion of cation exchange resins A low sodium intake may effectively potentiate the effect of other forms of treatment both surgical and pharmacologic

Drug Therapy The rationale for the use of drugs which lower blood pressure is based on the belief that prolonged marked elevation of systemic arterial pressure is in itself harmful and may contribute to and hasten the vascular lesions While this view is regarded with skepticism by some there can be no question but that there are well documented cases in which the use of depressor drugs has aborted or reversed progressive changes of malignant hypertension Furthermore there is evidence that patients with severe hypertension whose blood pressure has been effectively lowered by drug therapy over a period of 3 to 4 years may then be maintained on gradually decreasing doses and eventually no drug at all Since peripheral resistance is the most important of the factors which determine the level of the blood pressure hypotensive agents to be effective therapeutically should act by decreasing resistance rather than by decreasing cardiac output or flow The introduction of hypotensive agents with varying sites of action has provided the physician with a new approach to medical therapy of hypertension These drugs although effective require of the physician a thorough knowledge of the disease as well as of the agent employed In Table 119 are listed in some detail the important properties of five currently available hypotensive agents which the author believes to be worthy of trial when hypotensive therapy is indicated Others such as dehydrogenated ergot derivatives (dihydroergocornine) the nitrites and the crude veratrum viride derivatives (Veriloid) do not appear to be of similar value either because of lack of efficacy or because of the limited margin between the therapeutic and toxic effects The use of sodium thiocyanate and nitroprusside whose actions are similar has been found by some to be effective in the treatment of hypertensive headache and in lowering of arterial pressure Because of the necessity for controlling blood levels however their use is not widespread

Of the agents listed in Table 119 the ganglionic blocking agents are of extreme and unquestioned potency Their side effects however as well as the need for careful control by frequent blood pressure readings suggest that their use should be relegated to the severer forms of hypertensive vascular disease The uncertain absorption from the gastrointestinal tract of the first three blocking agents listed in the table constitutes an additional difficulty although this particular objection appears to be overcome by Inversine which is completely absorbed In the author s own experience protoveratrine particularly in combination with Apresoline and reserpine has produced gratifying results in moderate hypertensives In other hands particularly in severe hypertensives the combination of the newer ganglionic blocking agents and Apresoline with or without reserpine has produced effective remissions It should be stressed that the increase in renal blood flow which occurs with Apresoline is not entirely consistent and that it results in part from increased cardiac output in which the renal share of the cardiac output may be actually decreased The prolonged use of Apresoline

Table 118 OPPOSITE VIEWPOINTS ON THERAPY OF HYPERTENSION

The exact level of the blood pressure may have little clinical significance since it correlates poorly with the incidence of vascular disease and with mortality figures Treatment of hypertension per se is unjustified	The level of diastolic pressure may not correlate with vascular disease or mortality in the individual but in a large series it can be statistically shown to shorten the life span
Spontaneous remissions of hypertensive vascular disease tolerance of it and response to nonspecific therapy make results of specific hypotensive therapy difficult to evaluate	In spite of the variables irreversible fatal vascular disease may result from essential hypertension There is reason to believe that elevation of the diastolic pressure contributes to this and in the absence of knowledge of other factors and with the ability to lower blood pressure with specific therapy attempts to lower pressure seem justified in properly selected cases
The dangers and side effects of specific therapy may be worse than the natural course of the disease	Various effective forms of hypotensive therapy exist including psychotherapy It is justifiable to apply mild therapy to mild forms of hypertension and since the problems and dangers of therapeutic methods increase with increasing order of efficacy they may be justified in severe forms of the disease In experienced hands specific forms of therapy even though dangerous need not be delayed until irreversible changes have taken place

be remembered that the confidence patience and enthusiasm of the physician are important ingredients in any form of therapy The hypertensive process being what it is this factor undoubtedly accounts in large part for the varying degrees of success achieved by different investigators with the same therapeutic program

Symptomatic Therapy Improvement in symptoms as well as blood pressure levels frequently results from adequate psychotherapy (see below) For the relief of hypertensive headache elevation of the head of the bed during the night is usually beneficial Thiocyanate salts have been used with some success although the necessity for carefully checking blood levels of this drug to prevent toxicity has greatly decreased its usefulness Not infrequently a cup of black coffee or the administration of 200 to 400 mg of caffeine as the citrate or sodium benzoate salt given on arising may help the hypertensive headache Periodic venesection has met with occasional success in alleviating headache and dizzy spells Small amounts of sedation in properly selected patients may be of some value They should be carefully evaluated after preliminary therapeutic trial for the undesirable side effects With renal failure the short acting barbiturates Seconal and Amytal are preferable to phenobarbital since they do not require the renal route for their excretion Because sedation may play a more fundamental role in hypertension than that of symptomatic therapy its use becomes a highly individualized problem The administration of 30 mg of phenobarbital three to four times a day to one patient may well dull the knife edge of anxiety and result in improvement In other individuals the mental confusion that may result as well as the necessity for taking medication continually may do more harm than good The conscientious executive faced with a problem which he is capable of solving with a clear head does not benefit his hypertensive disease by grappling with his problem under the influence of sedatives which cloud his thinking Such situations must be carefully assessed on their individual merits The tranquilizing agents (Miltown Equanil) may be useful in allaying anxiety and tension without impairing critical faculties

Psychotherapy A majority of patients with essential hypertension have disorders of personality which may be aggravated by environmental or emotional stress resulting in conflicts and anxiety which may be correlated with fluctuations in blood pressure Although there is little agreement on the specific personality patterns involved such emotional contributions may be recognized frequently they are particularly evidenced in the tense anxious individual with marked fluctuations in blood pressure In such cases psychotherapy alone has produced results equal to the best of other forms of therapy It is moreover an indispensable adjunct to them Intensive psychotherapy may not be necessary and indeed should not be undertaken unless it can be followed to completion since the early part of the exhaustive psychiatric approach may often be followed by exacerbation of hypertension One should not underestimate the value of the psychotherapy resulting from a good physician patient relationship It is probable that just this resulted in the improvement in hypertension attributed to nostrums such as watermelon seed and garlic It follows from this example however that

may give rise to a syndrome resembling rheumatoid arthritis and disseminated lupus erythematosus This appears to be reversible with cessation of therapy and should not necessarily limit its usefulness

Dramatic and unquestioned therapeutic results have been obtained with the use of these substances They are toxic and dangerous in excessive dosage however and the margin between the toxic and the therapeutic dose is relatively narrow hence all such therapy should be begun in the hospital The hypotensive agents selected should be administered initially in less than effective dosage and increased slowly until either the desired therapeutic effect or toxicity supervenes As with insulin therapy it may be wise under controlled conditions in the hospital to familiarize the patient with mild toxic effects so that they can be recognized Alternate dosage with the initial agent and one of the others or preferably the potentiation of the depressor effect of the initial agent by the addition of small doses of another drug may increase the depressor effect while decreasing the side effects inherent in both Such a combination too may minimize the effect of tolerance to either agent Experience suggests that the concurrent use of two or three of these agents with different sites of action may be the method of choice When the patient s dosage has been established in the hospital he may be seen at less frequent intervals on the outside and the therapeutic effects may be increased without increasing toxic effects by the addition of a third agent or by the substitution of a new agent for one of the two when tolerance becomes apparent Potentiation of depressor effect can be achieved also by decreasing the sodium content in the diet Cessation of therapy should never be abrupt, since dangerous hypertensive rebounds may result The necessity for carefully controlling the use of these agents carries with it the disadvantage of making the patient drug conscious and blood pressure conscious Once he has become familiar with the drugs however and confident of their therapeutic benefits he may learn to regulate them by taking his own blood pressure in the same manner that an intelligent diabetic regulates his insulin by testing his urine

The presence of advanced renal failure contraindicates the use of the drugs listed here with the possible exception of small doses of Dibenzyline (10 to 20 mgm t i d) This appears to be useful in hypertension with renal failure possibly through its action on unexcreted pressor amines In mild renal failure large doses of reserpine (2 to 5 mgm per day) or the combined use of ganglion block and Apresoline may be of value In properly selected cases an initial increase in nitrogen retention may be followed later by improvement in renal function although at considerably decreased blood pressure levels

Surgical Therapy In the past interruption of the autonomic pathways by sympathectomy particularly by the lumbodorsal technique of Smithwick, has produced a convincing decrease in mortality in some severe cases of hypertensive vascular disease This treatment should probably be reserved until after drug and/or dietary treatment has been tried and failed or been rejected In this sense its value has the same relationship to medical therapy as does the surgical treatment of peptic ulcer Undesirable side effects of sympathectomy are postural hypotension and disturbance of sexual function in the male Renal failure cerebral vascular accidents and congestive heart failure are contraindications Bilateral total adrenalectomy as a treatment for hypertension is still in the process of evaluation but may be of value in intractable congestive heart failure with minimal renal functional impairment

Pyrogens It has been reported that a prolonged course of high fever induced by the intravenous administration of pyrogens may be effective in some cases of malignant hypertension This is drastic treatment for a drastic disease state and should be carried out only under the supervision of those with some degree of experience in this technique

Treatment of Hypertensive Encephalopathy The incidence and clinical picture of hypertensive encephalopathy has been described earlier in this chapter Although in certain cases hypervolemia may contribute greatly to the abnormality the common denominator is hypertension due largely to generalized vasospasm It is rational therefore to attempt to lower the diastolic blood pressure by pharmacologic means This may be done effectively in children and in a small percentage of young adults by the intramuscular injection of a 50 per cent solution of magnesium sulfate in doses of 0 2 ml per kg of body weight This may have to be repeated several times at 4 hr intervals to keep pressure at satisfactory levels following which the oral administration of from 13 to 30 ml of 50 per cent magnesium sulfate two to three times a day may satisfactorily control the blood pressure If intravenous injection is necessary a 3 per cent solution of hydrated magnesium sulfate may be given slowly One hundred and fifty mg of the salt per kg of body weight is given over a period of 1 hr The effects of overdosage *(somnolence respiratory difficulty)* may be counteracted by the administration of a 10 per cent solution of calcium gluconate by vein Oxygen therapy sedatives and occasionally venesection and spinal tap may be useful Dramatic results have been observed with the use of intravenous or intramuscular Protoveratrine or with large doses (2 to 5 mg of parenteral reserpine) and with the continuous drip of an

Table 119 DRUGS USED IN THERAPY OF HYPERTEN ION

Di g	S te of a t on	Pl arn a o-dynan ı	Dosage *	Sp ıal ıı d t s	Cont a d catı	Side ffects
Hyd a oplth l e (Apresol e)	Ce t l vas dı lator + Adrei ergıc blockade	Vasodılatı In creas d r d ac outp t It ased r ral bl od flow (±) Tacl yca d a	Oral 10 200 r g 4 ı d Toleran e ++	A an adj t w tl etl o- ıı n o ı u d d Ir t s tı e	Coro y art ry d ase I pt ul ı ( )	(1) Arthrıtıs lupus ( ) Heada he edema sea tacl y d (3) Unopposed cl olınerg type a dity *Rx* (1) Stop d g (2) Antihis- *t m n s (3) Al m m hy d x de g ls*
Gaı glio c block ıng ag nts †	Block t nomı trans mıss on at g gl on	Sy rath t d ı asyr pa tl t fıbı tı n (o tho-tatıc hyp t n with c mpensatory t chyca d d ased ıı testın l mo tıl ty etc)		I derate to v r hyp t A dıcal y n p tl ectoı y ( )	Co onary a tery dıs as Arterıo ler sıs D ab tes Glaucoma P ostatısm	(1) Constıpation ıau l y pt m (2) U nary ret ntıon (3) Impotence *Rx* *D s d e (1) Cathar-t (2) Ure h l e*
C6 hexameth on m		P or ab o pt on (30%) f om GI t t	Oral 1 1000 mg 3–4 ı d SC 2 –100 mg (as l lorıde) q 4 8 hr			
Pentol um Ansoly n		Varıable abs rp-t n f om GI tract	O l 10 0 mg q 6–8 l SC ? 10 n g q 4 8 l			
Ecol d			O l 2–100 mg q l lr SC 2 10 mg q 8 hr			
Ir ers ne		C mpl t ab orp tıon	SC –10 mg q 8 12 hr			Tremor
Pr to at ne	St n lates affer ent d f vag l refle	Fall BP B ady ard a Ce b al esıst a Re al res sta e Ca d ac utp t u h nged	Or l 0 5 1 5 g p b k fast pl 0 mg p e lu ch a d upp IV 1 –1 9 µg kg IM 4–6 µg/kg q 6 8 h	Hyperten e encepl al p-athy Hyp te e p l n ry ede a	I tol ran Coro y art ry dısease ( )	(1) Ep gastrıc opp ss n n u e vom t g al v tıo ( ) A gı a ( ) (3) A hytl m as *Rx D cr d (1) At o p th ( ) Eph d e f hyp t ns*
Re e p rp as l (v tal I n alkal d f *R wolfi er pent*)	C tral datı e ffe t C t l l b t o f pressor efle es Dıre t perıph e al a c la t o ( )	C t al dat o Mıld hypote o In eased tes t al m t l ty M s F ll a t o e-qu es 3 6 d y	O l 0 1 0 5 n g t d Tole an e ±	A dj t t tl er drugs Al e ın labıle ne rotıc hy p ter sı es 5 mg da ly hypertens es w th renal fa lure	Eld ly de-p ess d pat nts	(1) Sed tıo ( ) D arrhea (3) B dyc dıa (4) N ghtm es ( ) Nas l ngest (6) We ght g as d pp t te (7) D p essı n *Rx D cr dose*
D ben ylın	Ad n g c bl kade Bl ks lat ng at bol am es (p ph p rl e)	P ts t n f ad n gı ıı d at rs ı ı th n o p n ph) M osıs O tl ost t ty ı t ns n	O l 0 1?0 mg q d T le a e ++	As adj t In hyp te on w th re l faıl	A gı a ı e t rıs	(1) Mosıs ( ) D y mo tl (3) Nas l ng t n (4) Imp t ( ) T hycardıa *Rx D cr d*

T l ra ++ d tes t g l k l hood tl t tl dos w ll t ally eed to l n eased d t n ta a gı ff t
† Cl l tt a l (D l) a l u t g t wh h app rs to be t m ly ffect nd pe d t f ts t r tı ff t th pote tat of th asod ı esso ffects f th agents p t ula ly th ga gl l lock rs

cially palmitic acid whereas in the plasma unsaturated esters predominate

In the last decade Groen Kinsell Ahrens and Bronte Stewart have shown that in man blood cholesterol levels rise whenever the ratio of saturated to unsaturated fats in the diet rises even with constant total fat and cholesterol content of the diet Cholesterol is constantly being synthesized in the tissues of all animals cholesterol is excreted and reabsorbed from the bile The normal person pours 1 5 Gm of cholesterol into the gut on a low fat diet and reabsorbs about 1 2 Gm On a diet rich in fat but cholesterol free bile flow is increased and reabsorption may exceed 2 Gm Since it takes six eggs to provide 2 Gm of cholesterol it is perhaps not surprising that cholesterol added in modest doses to human diets raises the blood level so little If esterified with unsaturated fat such as corn oil there may be no rise in blood level from such a regime although esterified with inert saturated fats such as palmitic or stearic from butter or synthesized from excess carbohydrate the cholesterol provided in the bile might permit the maintenance of elevated plasma levels

Actual experience in laboratory study of animals and field surveys of human populations shows that diet is the essential basis of atherosclerosis On a starvation level of protein and carbohydrate no one will get the disease on the high animal fat intake of the American Army coronary disease is ten times as frequent as in men under thirty five years old in armies living without milk cream butter or eggs

Atherosclerosis can occur whenever the diet is as rich in cholesterol and saturated fat as is whole milk but the rate on such a diet and the blood lipid composition will vary enormously with endocrine and other metabolic factors the site of deposition will also vary at any given level of blood lipid in different people

During the years of active sex gland function women form more gallstones than men and white men and colored women have more severe coronary atheroma than the opposite sex Aortic atheromatosis shows little sex difference in humans or in chicks But cockerels on cholesterol rich diets have more severe coronary disease than hens of the same age and this process can be retarded by estrogens which have no influence on aortic lesions

It is a curious fact that the regimes which raise blood cholesterol and cause lipid deposition in the intima also hasten blood clotting retard fibrinolysis and predispose to thromboembolic disease Since many clinical episodes due to vascular obstruction result from thrombosis on atheromatous plaques and some pathologists consider mural thrombus formation important in the genesis of atheroma it is worth noting that postoperative thrombosis and embolism decreased in parallel with coronary disease during wartime food rationing in Norway and that both rose sharply after realimentation " In Asiatic cities where coronary disease is rare thromboembolism also is uncommon A high fat meal especially one rich in saturated fatty acid shortens the clotting time for many hours and the diet which lowers alimentary hyperlipemia and blood cholesterol will also protect against intravascular clotting Thus diet is doubly important in causation and prevention of the commonest and most fatal form of vascular disease—coronary occlusion

Local factors obviously play a great role in atherosclerosis for we see young men dead of severe coronary disease with no visible lesion elsewhere and elderly women with ulcerated extensive aortic disease and only a few small coronary plaques Intimal thickening whether inborn as in the epicardial part of the coronary arterial bed or acquired as in syphilitic mesaortitis or in the small arteries of the shrunken pyelonephritic kidney predisposes to rapid local deposition of lipid when plasma lipid levels are abnormal Even at birth the coronary arteries of human beings and of other mammals have remarkable intimal struts or cushions as thick or thicker than the media and far thicker than the intima in any arteries of the same caliber elsewhere in the body These struts are more developed in males than females even at birth They vary greatly from individual to individual and undoubtedly explain the great predisposition of coronary vessels to atherosclerosis

HYPERTENSION AND ARTERIOSCLEROSIS

When animals are put on regimes which cause atherosclerosis lesions develop more rapidly in those made hypertensive by renal embarrassment or other experimental techniques People with pulmonic hypertension have relatively severe atherosclerosis in the arteries going to the lung whereas in most people with pulmonic pressures one fifth as high as systemic the arteries of the lung show few or no lesions even when the aorta and its branches are seriously impaired Yet hypertension alone with low plasma lipid levels causes no atherosclerosis in men or animals

It is especially in the small arteries of the kidney and the retina that we see severe lipid deposition in hypertensives with high blood lipids although normotensives with the same chemical defect show few or no lesions in small arteries Diabetics on insulin and the usual (high) American levels of fat and salt intake show far more severe precocious arteriolar and even capillary and venular lesions of the retina and of the kidney than do nondiabetics In the retina the arteriolar lesions

aqueous solution of Arfonad a rapidly acting short lived ganglionic blocking agent whose effect by this route can be easily controlled by the rate of the drip

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228 ARTERIOSCLEROSIS

William Dock

The media of the arteries of men and animals show varying degrees of loss of muscular and elastic elements as age advances and with this the vessels become tortuous and dilated This change affecting temporal and splenic arteries and the aorta may be well advanced by the fourth decade of life A similar change in the walls of the veins predisposes them to varicosity and to formation of hemorrhoids But in the arteries neither this medial change nor medial calcification which is less frequent and occurs later in life leads to occlusion of the lumen or rupture of the wall The involutional changes in the media have few or no clinical sequelae

When age or involution of parenchymal or muscular organs leads to atrophy or in the brain to progressive loss of neurones the vascular bed atrophies and the intima proliferates A lumen adequate for the needs of the shrunken organ remains but intimal thickening free of lipid and physiologically harmless may lead the unwary pathologist to ascribe atrophy to arteriosclerosis This is most often said of the cerebrum in the uterus or ovaries atrophy is accepted as a normal concomitant of aging and not blamed on the obvious regenerative intimal thickening

All the changes mentioned above are seen in aged mammals they are usually bilaterally symmetrical and widely disseminated or diffuse This contrasts strikingly with the patchy atheromas lipid rich intimal thickenings which occur very rarely in aged wild or domestic animals or even in primitive or very poor populations but are apparent in the bodies of most prosperous people on the diets usual in North America and Western Europe by the age of forty As noted by Lober the process of lipid deposition in the intima of coronary arteries begins with suckling and in our culture continues throughout life In rabbits and in most human populations lipid deposition ends with weaning and the deposits are reabsorbed during growth During suckling blood cholesterol rises in man or rabbit from the natal level of 60 mg per cent to 180 mg per cent or higher and in rabbits reverts to the neonatal level on weaning In human populations living on grain vegetables fish and lean meat the levels run from 120 to 180 mg per cent rising over 200 after maturity

DIET AND ATHEROSCLEROSIS

In rabbits and chicks it is easy to raise blood cholesterol and start lipid deposition which progresses to atherosclerosis merely by adding cholesterol to purely vegetable diets In dogs rats and monkeys it is necessary either to destroy the thyroid or deplete the protein stores or to add large quantities of saturated fat to the usual diet before added cholesterol will sharply elevate blood cholesterol and cause gross atherosclerosis In these species high fat diet thyroid ablation or protein depletion alone will not cause the changes in plasma or intima—cholesterol must be fed in adequate quantities These animal experiments were initiated because it was obvious to clinicians and pathologists by the dawn of the twentieth century that neither cholesterol gallstones nor atheromatous vessels were encountered among poor or primitive people as often as among the rich or among vegetarians as often as among pastoral people who consumed milk in large quantities throughout life

Just as gout is associated with high plasma urate levels and with rich diets atherosclerosis is associated with high plasma cholesterol levels and diets rich in animal fat and cholesterol The lipid in the atheroma is cholesterol plus lecithin cephalin and sphingomyelin in about the same ratio as these are found in the beta globulin fraction of the plasma and with much less lecithin than in the alpha globulin fraction The cholesterol in the plaques is mostly esterified with saturated fatty acid espe

salt and calories is essential to prevent disease in many cases controlled by insulin

When arteriosclerosis removes people from active life after the period of maximum fertility has passed it benefits the young It relieves them of the care of parents or brings them an inheritance as they enter adult life But this biologic blessing must be paid for later for the way to avoid this disease is to have and to be responsible for long lived ancestors In an urban society this tends to favor late marriage and few or no children The high incidence of arteriosclerosis in the social group which has longest urban existence—the Jews—is to be correlated with their maintaining the dietary taste for dairy products and with the biologic advantage of losing parents who have passed the age of sixty Any attempts to eradicate such a disease from an urban population will be frustrated by natural selection and the survival of more grandchildren in families with few living grandparents Those best fitted to survive in a world growing more urban are those whose parents and in laws vanish and leave a nice nest egg as soon as possible after the children reach marriageable age Atherosclerosis and neoplasia are now the chief factors in determining that we do not overstay our allotted span of life too long

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229 DISEASES OF THE AORTA

Ben Friedman

CONGENITAL ANOMALIES OF THE AORTA

Some congenital malformations of the aorta are entirely benign others are incompatible with life beyond the intrauterine stage Symptoms can be attributable to three fundamental defects

1 *Obstruction or limitation of the blood stream* due to atresia stenosis and coarctation These are discussed in Chap 225

2 *Admixture with unoxygenated blood* resulting in cyanosis and hypoxia This may arise from a persistent truncus arteriosus from aortic atresia with a patent ductus arteriosus and from partial or complete transposition of the aorta The tetralogy of Fallot and the Eisenmenger complex are the only conditions in this group likely to permit life to adult age (see Chap 225)

3 *Compression or displacement of mediastinal structures* by vascular rings" These anomalies of the aortic arch may occur as isolated defects or in combination with other malformations They derive from the embryonic aortic arch pattern which encircles the primitive foregut Complete and incomplete forms are observed with the descending aorta lying either to the right or to the left of the mid line In the complete type a functional double aortic arch encircles the esophagus and trachea Variation occur in which portions of the right or left arch atrophy resulting in unusual origin and position of the major branches Most of these malformations are symptomless Dysphagia (dysphagia lusoria) hoarseness or respiratory distress occasionally result from compression of the esophagus trachea or recurrent laryngeal nerve by an anomalous subclavian artery which courses behind the esophagus by undue tension of the ductus arteriosus and pulmonary trunks or by a double aortic arch The abnormal position of the aorta and the anterior displacement of the esophagus and trachea can be detected readily by means of the fluoroscope Symptoms can sometime be relieved surgically

can be seen evolving and we know that hypertension or diabetes may precede vascular disease for years and may regress when hypertension or diabetes is controlled. *Here there can be no question* as to which comes first

EFFECTS OF EXERCISE AND OF SMOKING

There is rather impressive statistical evidence that men doing work which imposes muscular exertion have a later and lower incidence of coronary disease than those *on the same sort of diet who* lead sedentary lives. There is similar evidence of lower and later incidence of coronary disease in men and especially in women who do not smoke as compared to pack a day smokers of the same sex. Even in short term experiments physical activity lowers blood cholesterol but there are no convincing studies proving that smoking raises the level. *It is obvious that the onset of clinical evidence of* coronary disease might be delayed by the collateral circulation which physical activity might favor or be hastened by vasoconstriction due to nicotine. There is striking evidence that smoking does upset the cardiac function of people with asymptomatic coronary disease and therefore might hasten clinical evidence of atherosclerosis affecting the heart. *Davis and his colleagues observed striking de*terioration in ballistocardiographic patterns of subjects with coronary disease when they smoked or absorbed nicotine. This occurred rarely in controls but in more than half of the coronary patients. It seems safe to regard lack of exercise and the use of tobacco as accelerating the onset of atherosclerotic disorders but there is no evidence that either can *of itself damage the arteries*

STUDY AND MANAGEMENT OF ARTERIOSCLEROTIC SUBJECTS

The presence of clinically significant arterial disease is disclosed only by seeing retinal lesions or detecting functional impairment of legs kidney heart viscera or brain which is associated with a clinical picture such as angina known to be due in most cases to arterial obstruction. Other vascu*lar disorders must be ruled out and some dis*turbance of plasma lipid demonstrated before progressive disease can be ascribed to atherosclerosis. *In the brain arteriosclerosis cannot be diagnosed* on the basis of impaired mentation personality change or the like. These may be due to involutional loss of neurones or to metabolic defects—pellagra myxedema lack of cobalamin being well recognized causes of what passes for cerebral arteriosclerosis. A focal lesion affecting sensation motion or some discrete cerebral area suggests atherosclerosis or embolism. In the case of the heart angina (in the absence of aortic valve lesion or paroxysmal hypertension) or myocardial infarction is associated with severe atherosclerosis in *nearly 90 per cent of patients. In the legs inter*mittent claudication and gangrene in more than half the cases are arteriosclerotic in origin

When the question of severity and extent of this disorder is raised careful history and examination suffice to indicate degree of damage done in various regions, and x rays may show calcific lesions in the aorta and the legs. But even meticulous study *will not detect any large proportion of the coronary* arteries which will become occluded in a few hours or years. It can however be predicted that those with bad family records of vascular accident those with high blood cholesterol and those with hypertension will in any given decade have far more vascular accidents than those without these signs. This fact is of importance to insurers but when *the doctor talks to a patient no good is done by* stressing bad prognosis unless it leads the patient to accept effective therapy or prophylaxis. The arteriosclerotic patient may live in comfort for years or survive a series of severe vascular accidents with unimpaired earning power and morale; he may become depressed and disabled by the thought of imminent death or invalidism if risk of *arterial disease is described to him*

Many patients with severe arteriosclerosis of the abdominal aorta or its large branches may be completely cured by surgical excision and replacement by graft or prosthesis. Others may have their disability moderated by drugs. The cholesterol level may be lowered markedly by sitosterol feeding at mealtime by use of chelating agents or by thyroid *extract triiodothyronine or triiodothyroacetate*. In men and in women past the menopause estrogen *therapy may lower the beta globulin cholesterol* fraction. But the physiologic *management would* appear to be weaning from dairy products and use of a diet based on lean meat skimmed milk fish and vegetable products

If cholesterol falls in 3 months continuation of the regime for life can be urged for those who would prefer long life to rich fare. Low salt diet can on the same grounds be recommended for *trial by the hypertensive person* and more drastic therapeutic endeavors when the threat to life or vision becomes more apparent. Lecithin inositol *choline potassium iodide vitamins and supervita*mins have failed to lower cholesterol levels. The value of sitosterol or of chelating agents such as versene *in lowering cholesterolemia in any given* case can be determined only if the diet and weight are kept constant while the agent is being tested. *In the hypothyroid person specific therapy post*pones vascular disease; in the diabetic patient the type of diet described above with restriction of

sionally to hypertension and uremia due to renal ischemia

Syphilis is the commonest known cause of chronic obstruction of the origins of the major arterial trunks in the aortic arch It is observed in association with diffuse or fusiform dilatation of the aorta more often than with saccular aneurysms The manifestations may vary ranging from symptomless anisosphygmia to complete obliteration of the subclavian and carotid pulses (*pulseless disease*) Syncopal seizures visual impairment and trophic alterations in the lens and iris may appear but collateral circulation is usually sufficient to prevent severe ischemic changes In rare instances prominent collateral arterial channels may develop over the chest similar to those observed in coarctation of the aorta except that the direction of flow is reversed (reversed coarctation) Diastolic murmurs of extracardiac origin may sometimes be heard over partially occluded vessels at the base of the heart Nonsyphilitic causes of the chronic obstructive aortic arch syndrome which have to be considered in differential diagnosis are healed dissection of the aorta trauma polyarteritis and arteritis of unknown cause (*Takayasu's disease*) which affects young females predominantly

Aneurysm may also result from arteriosclerosis cystic medial necrosis or congenital malformations With rare exceptions patients with syphilitic cardiovascular disease will have corroborative evidence of syphilis either by history or serologic tests in blood or spinal fluid or by physical signs apart from the cardiovascular system Treponemal immobilizing antibodies may be detected in the blood of subjects in whom reagin cannot be demonstrated by conventional tests Arteriosclerotic aneurysms are more likely to occur in the descending aorta and seldom erode bone Advanced syphilitic aortitis is frequently accompanied by extensive atherosclerosis which may be reflected radioscopically in disproportionate calcification in the ascending aorta Arteriosclerotic aneurysms of the abdominal aorta usually occur below the renal arteries syphilitic aneurysms occur generally at or above the renal arteries.

Widening of the aorta is best demonstrated by roentgenography For this reason examination of every syphilitic patient should include fluoroscopy and x ray of the aorta Expansile pulsation is sometimes dampened by intraluminal clots and periaortic inflammation thus presenting an appearance which simulates a nonvascular tumor Visualization of the aortic lumen by aortography can be of great help in differential diagnosis

Treatment of patients with cardiovascular syphilis concerns itself first with management of the complications such as congestive heart failure and angina pectoris It is probably wise to withhold treponemocidal agents until these complications are reasonably well controlled

It is generally agreed that antisyphilitic drugs administered in the early stages of syphilis will effectively prevent crippling cardiovascular manifestations later in life Once cardiovascular disease had become established there was no unanimity of opinion concerning the use of prolonged and potentially toxic chemotherapy However the effectiveness of penicillin in tertiary syphilis has influenced the decision in favor of specific treatment of all patients with cardiovascular syphilis (see Chap 153) Unfavorable reactions to penicillin treatment are uncommon in cardiovascular syphilis but can be particularly dangerous in patients with ostial stenosis When the presence of this type of lesion is suspected and particularly when angina pectoris cardiac enlargement or congestive failure occurs in the absence of aortic regurgitation or in disproportionate severity to a mild valvular insufficiency treatment should be initiated very cautiously employing preparatory bismuth subsalicylate in doses of 0 1 Gm weekly for a period of 4 to 8 weeks or starting penicillin treatment with minute doses which can be administered orally

Antisyphilitic treatment can be expected to kill spirochetes and relieve active inflammation It may relieve some of the symptoms and may retard progression of the disease but no amount of specific treatment will restore elastic tissue which has been lost An aneurysm once formed will persist and may progress because of local hemodynamic changes Attempts have been made to reinforce the wall of an aneurysm by wiring and electrocoagulation within the sac or by wrapping the outside with Polythene cellophane These procedures have had limited application and doubtful success At present the treatment of choice is surgical resection employing grafts where necessary

ARTERIOSCLEROSIS OF THE AORTA

Arteriosclerosis is the most common affection of the aorta The factors which are believed to contribute to its development are increased intravascular tension disturbances in circulating lipids affections of the nutrient vessels and the ill defined changes associated with aging (see Chap 46) The aorta usually becomes dilated elongated and tortuous Arteriosclerotic aneurysms are relatively uncommon and are more likely to affect the descending aorta Intimal changes range from microscopic deposition of lipid material to pronounced thickening and formation of large atheromatous nodules or plaques Secondary changes may develop in the form of necrosis small hematomas calcification and ulceration.

Arteriosclerosis of the aorta is generally symp

SYPHILIS OF THE AORTA

Treponema pallidum is unique among parasites in its predilection for the aorta. The incidence of aortic involvement in large groups of untreated syphilitics has been estimated to be between 70 and 95 per cent. The earliest lesions consist of perivascular inflammation and endarteritis of the vasa vasorum in the adventitia and media. Medial necrosis, fragmentation of elastic and muscle tissue, and scarring follow. The loss of elastic tissue results in dilatation varying from slight localized or diffuse widening to huge aneurysms. Occlusion of the lumen of large arterial branches may arise from a combination of inflammatory swelling, cicatrization, thrombosis, intimal thickening, and secondary atheromatosis. Gummatous aortic lesions are rare.

Clinically demonstrable syphilitic cardiovascular disease rarely occurs in individuals who have had syphilis for less than 10 years or in those who had even a moderate amount of antisyphilitic treatment in the early phase of the infection. Its incidence is highest in the fourth and fifth decades of life, in males, and in Negroes.

The manifestations are determined in part by the distribution of the lesions. *Angina pectoris* and *aortic insufficiency* arise as the result of involvement of the root of the aorta, at the site of the coronary ostiums and at the insertions of the valves. Both of these crippling lesions may be influenced by congenital anatomic peculiarities, the first by an abnormally high location of the coronary orifices above the sinuses of Valsalva, and the second by an extension of elastic tissue into the commissures below the upper level of the cusps. The clinical aspects of aortic insufficiency and coronary ostial stenosis are described in Chaps. 223 and 224.

Uncomplicated aortitis is the commonest manifestation of cardiovascular syphilis and the most difficult to diagnose. Indeed, in its early phase it is a pathologic and not a clinical entity. Symptoms are singularly absent, and myocardial function is never embarrassed by aortic syphilis alone. The occurrence of angina pectoris, paroxysmal dyspnea, or cardiac enlargement denotes either syphilitic involvement of the coronary orifices or the valves or some independent complicating disease. The two most reliable signs of uncomplicated aortitis are aortic dilatation and the presence of a ringing tambourlike second aortic sound with or without a systolic murmur. Both signs are found in other conditions, such as hypertension and arteriosclerosis, and hence have little diagnostic significance unless these disorders are absent. Dilatation of the aorta in syphilis becomes apparent only when a sufficient amount of elastic tissue has been destroyed. Aortic widening can also occur with advancing age, in arteriosclerosis, and in hypertension. Similar auscultatory signs are frequent in hypertension, advanced arteriosclerosis, and in conditions giving rise to an overactive circulation.

Uncomplicated aortitis may be diagnosed in a patient known to have syphilis who has had little or no treatment in the early phase of the infection and who presents the auscultatory signs or widening of the aorta, especially in its ascending portion, if the disturbing complications listed above are absent. It is the exceptional patient who meets all of these criteria. The vast majority of cases of uncomplicated syphilitic aortitis cannot be recognized with certainty by present methods.

Syphilitic *aneurysms*, like aortitis, occur with diminishing frequency from the ascending aorta distally toward the abdominal aorta. They may be *single or multiple*, diffuse or sharply localized, fusiform or saccular, *smooth walled or filled with large organizing thrombi*. Aortic aneurysms burden the myocardium only indirectly *as a result of rupture* into or compression of the pulmonary *artery*, atrium, or *ventricle* or, as in the case of aneurysms of the sinuses of Valsalva, by distortion of the aortic valve cusps. Sudden death usually follows rupture with bleeding into the pericardium, bronchi, esophagus, or mediastinum. Many large aneurysms are surprisingly symptomless. In most instances chronic disabilities develop from compression, displacement, erosion, or interference with the circulation in neighboring structures.

The clinical picture is dependent on the size and site of the aneurysm and the direction in which it projects. Aneurysms which bulge anteriorly, particularly those located in the ascending aorta, are relatively asymptomatic, and signs when present are related to the mass itself, i.e., visible pulsations or pulsating tumors, widening of the area of percussion dullness, or shocks, thrills, and systolic murmurs at the base of the heart. In advanced cases the anterior chest wall may be deformed. Aneurysms of the arch and those pointing posteriorly and medially are more likely to produce symptoms and signs. Compression of bronchi attended by chronic cough, atelectasis, hemoptysis, and pneumonia recurring in one lobe frequently mimic the picture of malignancy. Confusion is often increased by evidences of impingement on neighboring structures, such as hoarseness from paralysis of the recurrent laryngeal nerve, phrenic nerve palsy, dysphagia, or venous distention in the neck, upper chest, and arms secondary to compression of the superior vena cava. Horner's syndrome, radicular pains, bone erosion, and bone pain simulate metastatic lesions in the spine. A tracheal tug or marked inequality in radial and carotid pulsations points to aneurysm rather than tumor. Aneurysms of the descending aorta in the region of the diaphragm may give rise to annoying radicular pain and occa

sionally to hypertension and uremia due to renal ischemia

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Arteriosclerosis of the aorta is generally symp

tomless Rigidity of the vessel wall leads to an increase in pulse pressure manifested by a rise in systolic pressure the diastolic remaining unchanged or declining slightly Atherosclerotic changes in the abdominal aorta which compromise nutrient vessels of the lower cord may give rise to weakness in the legs or to paraplegia Many arteriosclerotic aneu rysms cause no difficulty except for the anxiety aroused by the palpable pulsating abdominal mass Arteriosclerotic aneurysms can rupture spontane ously usually into the retroperitoneal space or more rarely into the peritoneum This diagnosis should be entertained in any elderly patient with severe persistent backache accompanied by pallor and evidence of acute blood loss Frequently the pain radiates along the sciatic nerve or simulates renal colic Rupture into the intestinal tract can result in massive intestinal hemorrhage Perforation into the vena cava gives rise to the local and general hemodynamic signs of a large arteriovenous com munication

Thrombosis of the aorta may be secondary to trauma or to retroperitoneal inflammation or with out apparent cause It occurs more often at the site of an aneurysm an ulcerated atherosclerotic plaque or as a result of retrograde propagation of an embolus which has lodged at the bifurcation The symptoms depend upon the extent of the ob struction and the rapidity with which it develops Gangrene of the legs is more likely to occur after embolism A more common variety the *Leriche syndrome* develops insidiously often over a period of years This disorder is most frequent in young and middle aged males and is manifested by inter mittent claudication in the buttocks and thighs diminution in femoral pulses muscular atrophy weakness of the legs and occasionally by failure of penile erection The legs are usually pale and cool but unlike the situation in occlusive disease of peripheral arteries gangrene and trophic changes are rare except as terminal complications The thrombosis may extend to the mesenteric or renal vessels resulting in visceral infarction or uremia The development of collateral circulation in the abdominal wall sometimes gives rise to a picture which mimics coarctation of the aorta at an unusual site in which notching of the ribs is absent The thrombosed aorta can often be palpated as a hard pulseless cord Calcium deposits are generally demonstrable in the abdominal aorta in thrombosis and not in coarctation

An arteriosclerotic aneurysm may be identified roentgenologically by the presence of calcific densi ties which outline the dilated walls Changes in lumen in the lower abdominal aorta can be visual ized by special angiographic techniques employing intraaortic or intraarterial injection of contrast media

Recent progress in the field of vascular surgery has made it possible with acceptable risk to re construct or bypass the diseased aorta and major branches Aortectomy and grafting have largely replaced older methods designed principally to strengthen the wall It is the treatment of choice for the thrombosed aorta the symptomatic aneu rysm and the rapidly growing symptomless aneu rysm provided that the renal arteries are spared With improvement in techniques the indications for operation will probably be extended to include the asymptomatic aneurysm that is discovered on routine examination

DISSECTING ANEURYSM

Dissecting aneurysm of the aorta has been re corded on the average of once in about 380 ne cropsies It has been observed frequently as a complication in coarctation of the aorta and more rarely in pregnancy the *Marfan syndrome* (see Chap 261) and in atherosclerosis The disease is almost invariably associated with degeneration of the aortic media of the type described first by Erd heim as cystic medionecrosis This medial defect apparently provides a weak point into which vasa vasorum may rupture particularly under conditions of increased intravascular tension The hemorrhage may dissect proximally into the sinuses of Valsalva or distally along the entire length of the aorta and eventually perforate externally through the adven titia or reenter the aorta through an intimal rupture The whole circumference or only segments of it may be dissected some branches may be skipped and others which arise further downstream may be involved

The exact etiologic sequence is unknown Hyper tension is present in most cases and is probably an important contributory factor There is evidence that the primary disturbance may at times be oc clusive or inflammatory disease of the vasa vasorum The pathologic picture has been reproduced ex perimentally by destroying a segment of the adven titia rich in nutrient vessels Intimal rupture is not universally present and cannot be considered to play an essential role in pathogenesis

Dissecting aneurysm occurs predominantly in middle aged and elderly persons and affects males more often than females The symptoms signs and differential diagnosis are considered in Chap 4 The diagnosis can be suspected on clinical grounds The main features are the character of pain the evidence of interference with arterial flow in various aortic branches widening of the aorta and the evidence of terminal perforation The major features of the pain which when present help to distinguish it from myocardial infarction are the attainment of

peak severity at the onset its persistence and its wide radiation to areas seldom affected in infarction such as the back lower abdomen legs or testes If the patient survives the initial period the pain may subside spontaneously to reappear as the dissection progresses

The blood flow may be impaired in any of the branches of the aorta from the root to the bifurcation causing reduced or absent arterial pulsations in the arteries of the neck abdomen or extremities The manifestations may simulate a cerebrovascular accident ischemic myelopathy renal infarction with malignant hypertension mesenteric thrombosis pancreatitis bleeding peptic ulcer and peripheral embolization

Dyspnea and hemoptysis may mimic pulmonary infarction Myocardial infarction may occur in the rare instances when the dissection involves the coronary ostia

Distortion of the aortic valves gives rise to signs which simulate syphilitic aortic insufficiency and aneurysm Low grade fever leukocytosis and elevated sedimentation rate are commonly present Perforation of the adventitia may occur anywhere along the course of the aorta or its main tributaries resulting in hemorrhage into neighboring structures Perforation of the aorta near the root usually results in hemopericardium and cardiac tamponade The ensuing clinical picture resembles closely that of myocardial infarction with shock distended neck veins and widened area of cardiac dullness Although rupture into the pericardium may lead to S T segment and T wave changes the characteristic electrocardiographic pattern of acute myocardial infarction is absent except in the rare cases when the coronary ostia are involved by the dissection Pulsations of the sternoclavicular joints and the presence of unusual sounds at the base of the heart point toward aortic dissection The latter may be of three types (1) the to and fro murmurs of aortic valve distortion known not to have been present prior to the onset of pain (2) the periaortic friction rub (3) a variety of adventitious sounds probably produced by escaping blood

Pain followed within minutes or hours by signs of arterial occlusion suggests dissecting aorta rather than embolization from myocardial infarction When the cephalic trunks are involved unconsciousness results In the absence of hypotension or arrhythmia this would be extremely rare in myocardial infarction The maintenance of an elevated arterial pressure favors dissecting aneurysm rather than myocardial infarction However marked decline in arterial pressure can occur in both conditions The diagnosis is confirmed when rapid widening of the aortic shadow is detected on successive x ray films Angiocardiogram may reveal the distortion in the aortic lumen and corresponding thickening in the wall but the patient is usually too ill to permit such manipulations

Most patients die within a few days Prolonged survival in some cases for years has been reported in individuals in whom the dissecting process is directed along a plane close to the intima and terminates in one or more perforations back into the lumen of the aorta forming a multichanneled vessel This circumstance has suggested an operative treatment in which an opening is deliberately made between the normal lumen and the dissecting channel in the thoracic portion of the descending aorta At the same time the distal portion of the dissected channel is closed There is a rational place for the use of antihypertensive agents in this disease

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230 PERIPHERAL VASCULAR DISEASE

Eugene A Stead Jr

SYMPTOMS AND SIGNS POINTING TO PERIPHERAL VASCULAR DISEASE

History and Physical Examination

One should suspect peripheral vascular disease in a patient with the following symptoms and signs

1 Pain in an extremity which is induced by exercise and relieved by rest Pain which is influenced by posture is localized to one digit, is unilateral or is paroxysmal

2 Impaired pulsations of peripheral arteries
3 Abnormal color of the skin particularly when affected by raising or lowering of the part
4 Gangrene ulceration impaired nail growth scleroderma excessive calluses or paronychial infections
5 Abnormal pulsations enlarged veins or edema
6 Unusual warmth or coldness
7 Swelling atrophy or difference in length of extremities
8 Auscultatory evidence of arteriovenous fistula
9 Localized systolic murmur over a large peripheral artery
10 Cyanosis of digits when immersed in cold water
11 Peripheral neuritis

If the above signs and symptoms are absent peripheral vascular disease need not be considered

The arteries capillaries veins and lymph vessels may be involved separately or in varying combinations The disturbances may be from organic disease of the vessels or from abnormal constriction or dilatation caused by dysfunction of the autonomic nervous system

DISTURBANCES IN ARTERIAL FUNCTION

Special Points in History and Physical Examination

Arterial insufficiency causes disturbances in nutrition to the part The following points in the history and examination are to be noted

History of Sensitivity to Cold with Blanching or Cyanosis of Digits On examination the part with arterial insufficiency may be colder than the corresponding part of the opposite extremity

Symptoms of Muscle and Nerve Ischemia Pain which develops in the muscles of the foot or calf on walking and disappears on rest is called intermittent claudication If exercise is continued after pain is present the muscles may become tender In more severe ischemia of the leg pain may occur at rest and be relieved by dependency The pain of ischemic neuritis is severe and diffuse with severe exacerbations Sharp shooting pains may dart through the entire extremity The acute paroxysms are apt to occur at night

State of Peripheral Vessels Presence or absence of femoral popliteal dorsalis pedis and posterior tibial pulses is noted Gangrene of the digits may occur without disturbances in these pulses In the absence of a palpable pulse the skin may show no evidence of malnutrition

Murmurs over Peripheral Vessels Pistol shot sounds are heard over the major vessels when the diastolic pressure is low and the stroke output high Localized systolic murmurs are heard over areas of narrowing produced by either disease of the blood vessel or by external pressure When the vessel is narrowed the local points of stenosis produce a murmur similar to that heard in aortic stenosis If the diastolic pressure below the point of narrowing is low either because of poor collateral circulation or because of wide vasodilatation produced by exercise a continuous murmur may be heard With this exception and that of venous hums continuous murmurs are commonly the result of an arteriovenous communication

Blanching on Elevation Redness and Cyanosis on Dependency On elevation to a 90 angle the part becomes pale and at times white The extent of the pallor indicates the extent of the arterial insufficiency If only the toes or a part of a toe is involved the pallor is limited to the ischemic area The color returns slowly on lowering the part to *heart level* The pallor occurs on elevation because the blood in the capillaries and venules drains out of the part by gravity and because the effective arterial pressure is lowered by having to overcome the hydrostatic force of a column of blood extending from the heart level to the elevated part Some pallor on elevation will occur in a normal foot but the pallor of arterial insufficiency is much more marked

When the part hangs down the blood flow is increased temporarily over the horizontal position because the hydrostatic pressure is added to the pressure created by the heart The increase in arterial pressure is effective until the veins fill Then it is opposed by an equal column of blood on the venous side and the pressure differential between artery and vein returns approximately to the differential present in the horizontal position The minute vessels of the part being in a state of chronic injury because of an inadequate circulation are dilated When these vessels first fill they are red Varying degrees of cyanosis gradually develop because of the slow blood flow

Atrophic Changes in Skin and Edema The skin becomes thin and atrophic Slight edema with loss of normal wrinkles is common If the patient keeps the foot dependent day and night to relieve pain pitting edema may develop from the combination of a high capillary pressure from dependency and the damaged state of the capillaries caused by ischemia

Gangrene

Infection Devitalized tissue offers a good place for infection to spread When peripheral neuritis is present infection may be more prominent than ischemia Osteomyelitis may occur

Neurologic Examination Peripheral neuritis is a common complication of diabetes Buerger s disease periarteritis nodosa and arteriosclerosis may cause neuritis because of the interference with the blood

supply to the nerves In periarteritis motor paralysis as well as sensory loss and pain is common

Occupation There may be a history of unusual exposure to cold and dampness Use of the pneumatic hammer has been said to cause Raynaud s phenomenon

Determination of Cause of Arterial Circulatory Insufficiency If the findings are those of arterial circulatory insufficiency it must be determined whether the insufficiency results (1) from occlusive disease entirely (2) from overactivity of the sympathetic nervous system (3) from abnormal reaction of the blood vessels to cold, (4) from the effect of cold agglutinins or cryoglobulins on the physical state of the blood or (5) from a combination of mechanisms The constrictor effect of the autonomic nervous system may be removed by paravertebral block of the appropriate sympathetic ganglion with procaine or by release of vasoconstrictor tone by body heating In either method the subject, with body exposed is placed in a cool room (temperature 18 to 20 C) The body temperature may be raised by enclosing the trunk in a heating cabinet or by immersing two uninvolved limbs in water baths at 43 C for 40 min When vasodilatation is produced in the upper extremities by body warming or by blocking of the sympathetic ganglion the temperature of the digits rises rapidly to between 30 5 and 33 C If the temperature rises to between 27 and 29 C there is moderate organic vascular disease If no rise occurs or if the temperature falls advanced local arterial disease is present. Body warming is the simplest and most effective method of relieving vasoconstrictor tone in the upper extremities It fails occasionally in the lower extremities Therefore if full vasodilatation does not occur paravertebral block is indicated in the lower extremities

ORGANIC OBSTRUCTION

Balance between Vessel Obstruction and Vessel Formation Obstruction of a large artery is a strong stimulus for new vessel formation and collateral circulation The symptoms produced represent the result of the balance between these two processes Complete obstruction of the aorta below the renal vessels which occurs slowly may produce no symptoms or the picture of impotence and thigh claudication The extremities may appear normally nourished When skin involvement becomes marked, little blood vessels are usually thrombosed This may be primary small vessel endarteritis as in diabetes or it may be secondary small vessel thrombosis secondary to occlusions higher up Gangrene with normal pedal pulses indicates small vessel disease Intermittent claudication with normal appearing vessels and absent popliteal or femoral pulses suggests larger vessel obstruction, which is frequently segmental

Peripheral Arteriosclerosis The etiology and pathology of peripheral arteriosclerosis have been discussed in Chap 228 The history and physical findings are those of arterial insufficiency The diagnosis is based on the following factors

1 Age of the patient It usually occurs after fifty

2 Sex Males are more commonly affected than females

3 Diabetes The incidence of arteriosclerosis is increased in patients with diabetes

4 Evidence of arteriosclerosis is usually present bilaterally although the symptoms may be unilateral

5 There are no symptoms of arterial disease in the upper extremities

6 The arteries as seen by x ray are frequently calcified

7 In patients with diabetes the small vessels may be occluded although the larger vessels are only moderately diseased Local gangrene of the skin of the toes may occur even though the rest of the foot is warm

8 In patients with diabetes neuropathy is common

Thromboangiitis Obliterans This condition was described fully by Buerger in 1908 It is an obliterative vascular disease affecting chiefly the peripheral arteries and veins of males in early adult life The etiology is unknown It is more common in Jews The disease involves primarily the blood vessels of the extremities Involvement of other vessels occurs only after extensive lesions have developed in the extremities Usually the process begins in medium and small sized arteries and affects large arteries such as the femoral and brachial, only in the late stages and in severe progressive disease Veins are involved less commonly The lesion is a nonsuppurative panarteritis or panphlebitis and is segmental leaving normal vessels between diseased segments Thrombus formation follows in which recanalization may occur The lesions come in crops producing complete and usually permanent obstruction followed by the development of extensive collateral circulation The history and physical findings are those of arterial insufficiency or superficial phlebitis The diagnosis is based on these considerations

1 Age Onset is usually between twenty and forty five years

2 Sex. Males predominate in a ratio of 75 1

3 Race Half the patients are Jewish.

4 Migratory phlebitis preceding or accompanying arterial disease

5 Severe pain at rest from ulceration or from ischemic neuritis

6 Absence of calcification as seen by x ray

7 Small vessels of the hands may be involved Thrombosis of mesenteric coronary cerebral or renal arteries is not uncommon

Thrombosis Thrombosis of the larger arteries of the lower extremities is common in the natural course of arteriosclerosis and thromboangiitis obliterans Whether or not dramatic symptoms of acute arterial insufficiency appear will depend on the degree of collateral circulation which has developed Gradual narrowing of a major vessel may progress *unnoticed to complete occlusion because the symptoms* of arterial insufficiency may not develop until the collateral channels begin to thrombose

Embolus Emboli are usually fragments from more centrally placed thrombi The occurrence of sudden arterial insufficiency without physical findings of marked peripheral vascular disease generally indicates an embolus The common sources are

1 *Mural thrombus from the left atrium in a* heart with chronic auricular fibrillation

2 Mural thrombus from the left atrium in a heart with mitral stenosis and commonly but not necessarily with auricular fibrillation

3 Mural thrombus from myocardial infarction of the left ventricle or more rarely from acute or subacute myocarditis

4 Thrombi on valves from subacute or acute bacterial endocarditis

Less common sources are

1 Thrombi in the aorta or its large branches

2 Venous thrombosis in patients with a right left shunt from congenital heart disease

3 Venous thrombosis causing pulmonary embolization right heart failure and passage of clot through patent foramen ovale

4 Myxoma of left auricle

Emboli are likely to lodge at the bifurcation of large vessels A saddle embolus riding on the bifurcation of the aorta may cause circulatory insufficiency in both lower extremities The signs of circulatory insufficiency are usually considerably distal to the embolus because of the effectiveness of collateral circulation The degree of circulatory impairment caused by arterial obstruction and that caused by secondary arterial spasm cannot be de*termined on inspection* The effects of paravertebral block must decide this question The local examination reveals the symptoms and signs of arterial insufficiency Loss of motion and of sensation may occur rapidly Pain has been discussed on page 64 At first there is no pain at the site of the embolus but tenderness may develop after a few hours as the embolus sets up a local inflammatory reaction in the vessel

Exposure to Cold Trench Foot Extremities with normal blood vessels are injured by prolonged exposure to cold Dependency and wetness combined with cold cause tissue damage even though actual freezing of the tissues does not occur On warming the injury results in extreme vasodilatation with swelling of the part because the capillaries have been damaged Later true capillary flow in the skin may cease because of capillary stasis and thrombosis although flow continues through AV communications This gives the clinical picture of superficial gangrene in a warm part Whether complete recovery or gangrene occurs depends upon the extent of the injury Persistent tenderness because of *fibrosis and ischemic neuritis* may develop

Obstruction of Main Arterial Trunk by External Pressure or by Syphilitic or Dissecting Aneurysms Broad insertion of the scalenus anticus muscle with or without cervical rib is a rare cause of Raynaud s phenomenon or organic arterial occlusion The vascular disturbances may be reflex from compression of a portion of the brachial plexus At times trauma *from compression of the artery causes thrombus for*mation with or without embolic phenomena distal to the area of injury

Persons who sleep with their arms hyperabducted above the head or whose occupation causes them to work with their arms hyperabducted may develop numbness and tingling from occlusion of the subclavian axillary vessels Usually discomfort causes the arms to be moved to a different position but gangrene of the fingers has been reported in some cases

Syphilitic aneurysm or dissecting aneurysm may cause obstruction to the main artery supplying the limb

SPASM OF ARTERIES AND ARTERIOLES

Raynaud s Disease and Raynaud s Phenomenon *Raynaud s disease is idiopathic bilateral paroxysmal* contraction of the arteries and arterioles of the digits usually without local gangrene The primary fault seems to be a local sensitivity of the digital vessels to cold The attacks are precipitated by cold or emotion and are relieved by warming Raynaud s phenomenon consists of paroxysmal attacks of ischemia of the digits occurring in the course of other diseases such as scleroderma thromboangiitis obliterans cervical rib arteriosclerosis crutch paralysis and pneumatic hammer disease Diagnosis of Raynaud s disease from the history and examination is made from the following points

1 Sex Females are affected much more often than males

2 Age It is less common before puberty and after forty though it may occur at any age

3 Bilateral and symmetric involvement of digits It is more common in hands than in feet

4 Attacks of cyanosis can be reproduced by immersion of hands in cold water or by cooling the

body rapidly by a cool shower The digital arteries and arterioles contract The finger becomes blue if the minute vessels remain dilated pale if they contract On rewarming, reactive hyperemia occurs

5 If the disease is of many years duration small superficial areas of gangrene may occasionally be present

Diagnosis of Raynaud s phenomenon is made if the above findings are noted in conjunction with organic arterial disease scleroderma cervical rib or history of the use of a pneumatic hammer In the beginning it is frequently impossible to differentiate between benign Raynaud s disease and progressive scleroderma with Raynaud s phenomenon

Scleroderma This is a diffuse disease of the collagenous system with skin and visceral manifestations The etiology is unknown Raynaud s phenomenon is frequently seen before the characteristic skin changes occur In many instances the skin changes are localized to the distal portions of the extremities (acroscleroderma) The skin becomes board like and is bound down to the underlying tissues Decreased sweating increased pigmentation and calcification of the skin occur Gangrene of the digits with marked shortening of the phalanges is not uncommon (sclerodactylia) Involvement of the esophagus heart and lungs may occur early or late in the disease

Ergotism Spasm of the arterioles with thrombosis and gangrene is produced by ergot poisoning In past times it was seen in epidemic form as the result of the contamination of rye with ergot fungus (*Claviceps purpurea*) It is occasionally seen after the repeated use of ergot to induce abortion or after the use of ergotamine tartrate for pruritus

Reflex Spasm Any painful area in the extremities may cause symptoms and signs of ischemia from stimulation of the autonomic nervous system The ischemia of embolus or thrombus is intensified by reflex activity Ischemia from organic disease of the vessels from arteriosclerosis or from thromboangiitis obliterans may be intensified by active vasoconstriction mediated through the autonomic nerves

Disturbances in Small Vessels from Changes in Blood

Changes in the physical state of the blood may cause small vessel obstruction Patients with sickle cell anemia are prone to multiple thromboses The leg ulcers seen in this disease are probably an example of small vessel thrombosis on the basis of mechanical obstruction caused by the sickled cells When the titer of cold agglutinins is high exposure to cold may cause Raynaud s phenomenon The development of globulins which precipitate in the cold (cryoglobulins) in patients with leukemia or myeloma may also cause Raynaud s phenomenon

PROGNOSIS IN DISEASE OF ARTERIES

The prognosis depends upon the age of the patient the rate of progression of the primary disease and the degree of the development of the collateral circulation In *arteriosclerosis* the patients are elderly the coronary and cerebral vessels are apt to be affected by the disease and all the vessels of the extremities are usually diseased. Once gangrene develops, the chances of saving the extremity are not good

In *thromboangiitis obliterans* the prognosis for life is usually good If symptoms are present which indicate that visceral vessels are involved the prognosis becomes more guarded The chances of losing a limb are more difficult to estimate Fingers are occasionally lost the hand almost never One or both lower limbs are more frequently lost The clinical course is very variable In some patients there is no further progression after one or two episodes of arterial occlusion In others the disease is moderately progressive with long periods of relative quiescence between periods of arterial occlusion The progression of the disease exceeds the formation of collateral circulation, and eventually damage to the vascular tree is moderate to severe In time new lesions may cease to develop In certain patients occlusion of large arteries occurs with severe persistent arterial insufficiency or gangrene In a few the disease is rapidly progressive and gangrene develops in two or more extremities Some authors state that the disease does not progress if the patient stops smoking

In *arterial obstruction* from an embolus or thrombus the prognosis is greatly influenced by age and the general condition of the patient The embolus would appear to have the best prognosis because the peripheral arterial tree might be undamaged. However this assumption is modified by the fact that the embolus frequently comes from a mural thrombus caused by congestive failure or myocardial infarction and the mortality and development of gangrene in embolus and thrombosis are approximately the same

In *Raynaud's disease* as defined in this discussion the prognosis is good by definition Complications are rare and the digits are not lost In *Raynaud's phenomenon* accompanying other disease the prognosis is that of the primary disease Thus in scleroderma associated with Raynaud s phenomenon the outlook depends on the extent and rate of progression of the scleroderma. This is true whether the sclerodermatous changes are generalized or are still localized to the extremities

TREATMENT OF ARTERIAL INSUFFICIENCY

Chronic Arterial Insufficiency Since the etiology of arteriosclerosis and thromboangiitis is not known treatment directed toward prevention or removal of the primary factors is not possible In segmental obstruction of the femoral and iliac arteries intimal stripping and grafting offer new hope for improving the circulation

General Care Three points in general care should be stressed

LOW FAT DIET IN ARTERIOSCLEROSIS Many patients with arteriosclerosis have high serum cholesterol values There is evidence that the cholesterol levels can be lowered in many instances by a low fat diet if it is followed over long periods This offers the only direct approach to treatment of the arteriosclerotic process itself

DIABETES In any patient over forty with peripheral vascular disease the possibility of diabetes mellitus should always be remembered and a fasting blood sugar level determined even if there is no glycosuria

COMPLETE ABSTINENCE FROM TOBACCO The course of thromboangiitis is modified if smoking is stopped completely Many physicians are unwilling to assume responsibility for the care of a patient with thromboangiitis unless the patient consents to give up smoking entirely Most observers advise against smoking in arteriosclerosis although the adverse effects of smoking seem less certain here than in thromboangiitis

Care of Local Areas The care of the local area with circulatory impairment from arteriosclerosis thromboangiitis or damage from exposure to cold is similar The greatest danger is gangrene in the toes This is usually precipitated by *trauma infection* or *burns* all of which can ordinarily be prevented by good foot care Care of the feet means careful washing in tepid water at night keeping the skin pliable with lanolin use of a bland dusting powder to absorb perspiration use of warm finely woven woolen socks in winter careful cutting of the nails with the ends cut straight across to avoid ingrowing nails Epidermophytosis must be treated when present but strong ointments or solutions are to be avoided Soaking twice daily in 1 8 000 potassium permanganate solution is satisfactory Dry heat is contraindicated Remember that sensation may be impaired because of peripheral nerve involvement Heat above the temperature of the blood raises the temperature of a part with impaired blood supply much more rapidly than that of a normal part In this situation the blood acts as a cooling system to lower the temperature of the tissues if this cooling system does not function efficiently burns occur Heating the part by reflex vasodilatation is safe local heat may raise the metabolism without a corresponding increase in blood supply and precipitate gangrene The shoes should fit perfectly and should be broken in gradually If any break in the skin or blister occurs from any cause the patient should go to bed and call his physician Reflex vasoconstriction is to be minimized In the winter there is need not only for adequate protection for the part itself but also for attention to preserving the warmth of the body No local protection will keep the extremities warm if the trunk is cool and the body is attempting to preserve heat

Reflex vasoconstriction may accompany organic occlusive vascular disease If body warming or paravertebral block demonstrates release of reflex tone improvement of the circulation to the extremity by sympathectomy is indicated Some observers have reported improvement after sympathectomy even though paravertebral block caused no rise in temperature Sympathectomy may be followed by gangrene in advanced disease because it may divert the greatly limited supply of blood from the severely ischemic tissues to the more normal tissues of the part

Sympathectomy does not increase the flow of blood through muscles and has no direct effect on intermittent claudication If sympathectomy is performed in patients with intermittent claudication it should be more extensive than is necessary to release the vasoconstrictor tone of the vessels of the skin of the leg and foot A higher sympathectomy may be effective in increasing the circulation in collateral vessels by passing the areas of obstruction

Buerger s exercises are useful They have the disadvantage of being too tiresome to continue for a long period of time They help because when the foot is dependent the effective arterial pressure is increased until the pressure from gravity is counteracted by an equal column of blood in the veins The foot is emptied by raising it just far enough above heart level to produce collapse of the veins and slight pallor It is then returned to the dependent position The ideal conditions are (1) maximum lowering of the foot below heart level leaving it there until the veins are full and (2) the least elevation for the shortest period of time which will suffice to empty the foot When the valves of the veins of the legs are competent walking slowly is an effective form of Buerger s exercises The contraction of the muscles forces blood up the deep veins the venous pressure falls sharply as the muscles relax and the high arterial pressure produced by gravity is effective until the veins fill

Pyogenic infections of the feet and toes are common in patients with impaired blood supply This is particularly true if peripheral neuritis is present

If an apparently gangrenous part is warm infection is playing an important role and intensive penicillin therapy may greatly change the picture Each time the doctor must ask himself Is infection or ischemia the primary cause of the acute episode?

Acute Arterial Insufficiency In the acute circulatory insufficiency caused by thrombosis or embolus *immediate* and repetitive release of sympathetic tone by paravertebral blocks of the sympathetic chain is essential Tetraethylammonium bromide or Priscol may be tried if the necessary equipment for the paravertebral block is not at hand The coagulability of the blood is lowered by the immediate intravenous injection of heparin and after determining the prothrombin time administration of Dicumarol is started by mouth Heparin is continued at 4 hr intervals until the Dicumarol has lowered the prothrombin concentration to effective anticoagulant levels If the arterial insufficiency is the result of an embolus effective anticoagulant therapy must continue for approximately 3 weeks until there has been time for the site of the embolus to be covered with endothelium

Operative removal of an embolus may be considered if surgery is available in the first 8 to 10 hr In most instances the complicating heart disease or generalized vascular disease makes surgery inadvisable

The part should not be elevated The body should be heated but local heat should not be applied to the involved extremity Some authorities advise active cooling or even refrigeration of the part during the interval between the occlusion of the artery and the consideration of surgery

Raynaud's Disease The body should be dressed warmly so that the vessels in the hands and feet will dilate to help dispose of body heat The hands and feet should be protected with warm socks and gloves Minor episodes of "dead fingers" should not occasion alarm If these measures are not adequate Priscol given orally in doses of 25 to 75 mg every 3 or 4 hr is frequently helpful

Raynaud's Phenomenon Adequate heat to the body and protection of the extremities from cold and trauma are important The response of the underlying disease to therapy is more important than the treatment of the vasospasm When associated with scleroderma the prognosis is guarded Priscol has been reported to be effective in controlling the vasospasm Sympathectomy may be tried but the effect is usually temporary Testosterone has been reported to have a favorable effect in scleroderma when given for several months

Amputation The indications for amputation are (1) gangrene (2) uncontrollable infection (3) intractable pain and (4) such complete loss of function from deformity or contracture that the limb is a burden Amputation is a last resort, and conservative therapy has saved many limbs The site of amputation must be at a level where tissue nutrition is good In the last analysis the amount of bleeding at operation and the appearance of the tissues after incision determine whether the stump will be viable Usually clinical observation determines the level of the trial incision but special tests such as the appearance time of intravenous fluorescein and the effect of intradermal histamine may be helpful

DISTURBANCE IN VENOUS FUNCTION

Varicose Veins

Dilatation and tortuosity of the superficial veins of the lower extremities result from constitutionally defective valves affected by postural strain or from the enlargement of the superficial circulation to compensate for obstruction of the deep circulation The obstruction of the deep circulation usually results from deep thrombophlebitis Increased blood flow from an acquired or congenital arteriovenous fistula is a rare cause of varicosities

In a normal subject who stands motionless for a short time the hydrostatic pressure in the leg veins is equal to the height of a column of blood extending from the fourth rib to the level of the vein In a man 6 ft in height the pressure at the ankle is about 105 mm Hg Blood from the foot is returned by the force of the heartbeat and all of the valves are open These pressure relations are the same therefore in valved and nonvalved veins On contracting the muscles of the leg and thigh blood is forced up the extremity by the high intramuscular tension With normal valves it cannot be forced downward or outward into the superficial circulation through the communicating veins The blood in the superficial veins of the leg is not forced upward by the contraction because the skin tension does not exceed the hydrostatic pressure When the extremity is relaxed blood does not flow downward into the muscles because the valves control it Blood enters the veins in the muscles from the arteries and from the superficial veins by way of the communicating veins Backflow from the cava is prevented by valves and the runoff through the communicating veins lowers the pressure in the superficial veins effectively The fall in hydrostatic pressure in the venous system lowers capillary pressure effectively and prevents edema When the valves of the veins are destroyed the venous and capillary pressures are not lowered by exercise Chronic edema petechial hemorrhage poor drainage and infection frequently result

Varicose veins fall into the following groups (1) Simple dilatation of the veins with competent valves The lowering of capillary pressure by exercise is maintained and edema does not result Superficial venous thrombosis in the dilated tortuous vessels may be troublesome (2) Varicose veins with incompetent valves in the superficial veins but competent perforating and deep valves On walking the venous pressure is not lowered unless the superficial veins are prevented from filling from above by local pressure When the superficial veins are correctly obstructed by a tourniquet exercise effectively lowers the venous pressure (3) Varicose veins with incompetent valves in the superficial and communicating systems In many of these patients the varicosities have resulted from thrombophlebitis of the deep veins and the valves of the deep veins are destroyed Exercise has no effect in lowering the venous pressure when walking Brawny edema may mask the superficial varicosities and their extent is rarely realized until the venous tree is visualized by the use of Diodrast Intractable chronic ulcers are common (4) Rarely the deep veins are completely obstructed and the superficial veins are needed to return blood from the limb

Treatment of the first two groups by the combination of high ligation and injection of sclerosing solutions or removal by vein stripping is satisfactory The treatment of the last two groups is less satisfactory and prevention by more intensive treatment of the deep vein thrombophlebitis is the most satisfactory answer Destruction of the superficial varicose veins may be helpful even if the valves of the deep veins are destroyed because the varicose superficial veins are rarely necessary to return blood from the leg Once the condition is present it is beneficial to prevent edema formation by application of external force to counteract the effect of gravity Bed rest with elevation of the part allows healing The application of pressure bandages or of a jelly boot prevents the breakdown of the healed lesion when the patient is up One should remember the magnitude of the hydrostatic force one must counteract when the patient stands Ace bandages are rarely adequate a pure rubber roller bandage 3 in wide and 15 ft long is much more effective

Thrombophlebitis and Phlebothrombosis

Thrombus formation in veins is common Dilated tortuous superficial varicose veins frequently become tender and hard with redness of the overlying skin The inflammatory reaction usually subsides uneventfully and embolic complications are unusual Recurrent superficial venous thrombosis is a common occurrence in the natural history of thromboangiitis obliterans Local trauma from the administration of various solutions and medications is a not uncommon cause of superficial thrombophlebitis Again embolic phenomena are rare

Thrombus formation in veins occurs at times in all acute and chronic infections after operations and after childbirth It is common in patients with chronic debilitation heart failure or carcinomatosis and occasionally occurs in apparently normal persons Venous thrombosis is apt to occur contiguous to areas of local infection or trauma It is seen in the pelvis in puerperal infection and in the prostatic veins after prostatectomy In the majority of instances the thrombus begins in the deep veins of the calf and extends proximally The process may cause very little reaction in the vein wall (phlebothrombosis) and if this is the case the thrombus is particularly prone to break loose and lodge in the pulmonary tree On the other hand the reaction may involve the veins of the entire extremity with the inflammatory reactions extending into surrounding lymph channels (thrombophlebitis) With an extensive reaction the clot adheres tightly to the vein wall and then embolic phenomena are less common

The precise etiology of phlebothrombosis and thrombophlebitis is unknown Slowing of the blood stream seems to be an important factor in thrombus formation Acceleration of the clotting time probably plays a part The role of changes in the vein walls has not been determined In spite of the severe systemic reaction and the evidence of the reaction of inflammation in the extremity in the more fulminating cases no infectious agent has been found

Local symptoms may be absent A rise in pulse rate or an unexplained slight fever in a patient in bed may be the only sign of phlebothrombosis and the condition may not be recognized until an embolus has lodged in the pulmonary artery Several days later tenderness in one or both calves may occur Tenderness in the calf and pain in the calf on dorsiflexion of the foot may be the only sign If the foot is dependent slight edema and cyanosis may be observed Other findings may include a measurable although not always visible increase in the circumference of the calf as compared to the opposite leg slight prominence of the veins increased local warmth or diminished pulsation on the affected side and local pain on compression with a blood pressure cuff at a pressure of 80 to 120 mm Hg

At the other extreme is the painful swollen cyanotic leg of acute thrombophlebitis In this condition the arteries are not involved directly intense reflex vasoconstriction may occur however and at times the arterial pulse is felt with difficulty Fever and leukocytosis are present

Treatment is divided into three parts

1 Prevention of clot formation in the leg veins by early ambulation or by bandaging of lower extremities when the patient is confined to bed and by the use of heparin and Dicumarol

2 Prevention of pulmonary emboli after leg veins are involved Anticoagulant therapy is usually successful Pulmonary emboli continue in an occasional patient and ligation of both common femoral veins or the vena cava becomes necessary (Embolism and infarction of the lungs are discussed in Chap 236)

3 Prevention of destruction of lymphatic vessels and veins which leads to persistent edema and chronic ulcers Pain is relieved and edema clears more quickly when the sympathetic tone is released by repeated paravertebral blocks Anticoagulant therapy may reduce the number of vessels permanently thrombosed Elevation and proper bandaging will minimize the edema Particular attention to bandaging should be given when the patient is allowed to be up

DISORDERS OF PERIPHERAL LYMPHATIC VESSELS

Water and electrolytes which leave the capillaries can reenter the capillaries without difficulty Protein and various forms of particulate matter pass into the lymphatic capillaries If the lymphatic drainage to a part is blocked the extracellular fluid will gradually assume a high protein content The capillary filtrate may contain very small amounts of protein but as the water can be reabsorbed by the blood capillaries and the protein cannot an effective concentrating mechanism is present When the lymph vessels are normal lymph flow depends on muscular contraction respiratory movements transmitted movements from arterial pulsations and to a certain extent on gravity Complete immobilization of the lower extremity in a patient sitting in a chair leads to physiologic lymphatic obstruction

Acute Lymphangitis When bacterial infection in an extremity is not localized the inflammatory products pass proximally along the lymphatic channels The material carried in the lymph channels causes dilatation of the small blood vessels about the lymph vessels and their courses are outlined by one or more red streaks Before chemotherapy was available lymphangitis always carried a serious prognosis because it is a sign of uncontrolled spreading infection Immobilization of the part greatly reduces the rate of spread of the infection by reducing the rate of lymph flow With chemotherapy fear of lymphangitis and the surgery necessary with lymphangitis has largely disappeared

Chronic Lymphatic Obstruction Widespread obstruction of the lymph vessels may result from congenital or familial disorders of the lymph vessels The lymphedema of the familial type is called Milroy s disease Acquired chronic lymphedema results from obstruction of the lymph channels by neoplasm scar operative removal of lymph nodes and fibrosis caused by x ray therapy It may follow low grade lymphangitis from filariasis from lymphogranuloma venereum and from repeated streptococcal infections It may be a complicating factor in certain instances of severe edema following thrombophlebitis

In its early stages lymphedema cannot be distinguished physically from any other form of soft pitting edema On laboratory examination the high protein concentration separates it from cardiac and nephritic edema but not from the fluid of myxedema Lymphedema causes fibrosis in the tissues and in time the tissue becomes hard and brawny The skin may be thick and folded with indolent ulcerations

Treatment of Chronic Lymphedema Early and persistent therapy is important If marked edema is prevented by postural drainage by effective bandaging and by limiting upright activity to periods short of edema formation much of the fibrosis and recurrent infection will be prevented This program calls for persistence on the part of both doctor and patient Acute attacks of lymphangitis can be controlled by appropriate chemotherapy

LEG ULCERS IN PATIENTS WITHOUT PERIPHERAL VASCULAR DISEASE

In a normal subject an injury to the skin of the foot or ankle is much more serious than one to the hand or wrist In the ambulatory patient lesions on the lower leg and foot may heal slowly If healing does not occur promptly the patient should be put to bed and the part elevated If the lesion is allowed to become chronic low grade local phlebitis lymphangitis and arteritis develop Even if the main vessels to the part are unaffected these local changes cause poor tissue drainage and tendency to recurrent infection and ulceration A nonhealing nontraumatic ulcer of the lower leg is an emergency and requires bed rest until healing occurs

SPECIAL DIAGNOSTIC TESTS

The history and physical examination will establish the presence or absence of arterial insufficiency

When the circulation is normal no instruments are necessary to demonstrate the fact The skin shows no trophic changes and does not blanch abnormally on elevation The arterial pulses are palpable If the main artery is occluded by pressure for several min utes release of pressure will cause bright red re active hyperemia Heating of the body causes the extremities to warm and immersion of the part in hot water brings out the capillary pulse Histamine pricked into the skin produces a typical wheal and erythema When there is obvious arterial insuffi ciency these findings are changed as outlined under Special Points in History and Physical Examination When other signs of arterial insufficiency are pres ent it is not safe to attempt to demonstrate the capillary pulse by placing the involved extremity in hot water

Special tests have been of value in understand ing the normal physiology of the peripheral circu lation They have been of use in quantitating the degree of damage caused by pathologic processes and have aided our understanding of the develop ment of collateral circulation They have been use ful in determining in at least a semiquantitative way the effects of therapy in occlusive vascular dis ease

The following tests are useful at times

1 Measurement of skin temperatures in a cool room (18 to 20 C) before and after release of sympathetic tone When the blood supply is de creased by occlusive arterial disease or by reflex vasoconstriction or by both the extremities cool Release of sympathetic tone is accomplished by paravertebral block by spinal anesthesia or by raising the rectal temperature by body warming If the skin temperature does not rise the decrease in blood flow is the result of occlusive vascular dis ease A rapid rise to 30 5 to 33 C indicates normal blood supply An intermediate rise indicates both reflex sympathetic constriction and occlusive vascu lar disease This test has the virtue of simplicity and has proved to be of clinical use

2 Arteriography and venography The arterial tree may be visualized by x ray after the intra arterial injection of Diodrast The exact point of arterial obstruction and the pattern of the collateral circulation can be determined It is helpful in showing segmental occlusion in the iliac and femoral vessels These lesions can now be approached sur gically Visualization of the veins by the injection of Diodrast is occasionally useful

3 Circulation time to the extremities Several methods are available The fluorescein test is the most objective Three ml of a 20 per cent aqueous solution of fluorescein is injected quickly into the antecubital vein and the time of appearance of a greenish yellow glow in various parts of the body is observed When arterial insufficiency is present the appearance time of the fluorescein is prolonged In severe ischemia no fluorescein may appear

4 Oscillometer This is a volume recorder which magnifies the changes in volume which normally occur with each cardiac systole The ordinary blood pressure recording apparatus may be used as a crude oscillometer Refinements of the oscillometer have not increased its clinical usefulness

5 Histamine wheal test If the arterial circula tion is inadequate histamine pricked into the skin gives a subnormal or absent reaction

6 Measurement of blood flow by plethysmo graphic techniques has advanced our knowledge of the circulation but the method is not suitable for routine clinical use

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Section 3 The Kidneys

T R Harrison

The modern concept of renal disease began to develop as the result of the classic descriptions of clinical features by Richard Bright Among numerous others who made lasting contributions the names of Magnus Levy (disordered excretion of salt) Friedrich von Muller (concept of nephrosis) Volhard and Fahr (correlation of clinical and pathologic findings) Thomas Addis and Donald van Slyke (natural history of the renal disorders) and Homer Smith (development of methods of testing the various renal functions) are especially noteworthy

The reader will be aided in the interpretation of the discussion to follow by reviewing Chap 19 which deals with principles of renal function and with the important manifestations of renal disorders Pyelonephritis and cystitis are considered in some detail in Chap 144

Before discussing the specific diseases of the kidneys an attempt will be made to clarify certain topics which are frequent causes of confusion

231 GENERAL ASPECTS OF RENAL DISORDERS

John P Merrill

Diagnosis One generality at least may be stated that no particular alteration is characteristic of any particular form of Bright s disease—by whatever cause the end has been reached the organ structure of contracted kidneys is similar The clinician therefore need have no feeling of frustration if at the end he cannot differentiate one from the other by functional means This pronouncement by a pathologist serves to emphasize the fact that exact etiologic analysis of advanced renal disease may be difficult if not impossible not only with regard to manifest functional aberrations but even from the standpoint of the structural changes In advanced renal disease several common types of bilateral processes eventually tend to produce a single clinical picture which is characterized essentially by excretory failure with uremia and generally also by hypertension cardiac enlargement and vascular retinopathy If the patient is seen only at this stage it is often difficult and sometimes impossible to decide whether the initial process was glomerulonephritis nephrosclerosis or pyelonephritis Indeed the destruction of renal parenchyma that is begun as glomerulonephritis frequently is complicated by superimposed pyelonephritis To both of these entities in turn perhaps through the medium of hypertension may be added the changes of nephrosclerosis

From a practical standpoint the evaluation of the patient with frank renal failure should not concern itself primarily with the etiologic nature of the primary process Of much greater importance is the possibility of treatment or reversibility Once it has been ascertained that excretory failure is due to irreparable structural changes treatment at best must be aimed at the containment of the metabolic derangements and the prevention of further renal damage When however there is a possibility that obstruction infection or acute reversible renal damage is responsible for the excretory failure a judicious therapeutic regimen may prolong life sufficiently for the injured kidneys to show marked spontaneous improvement Thus the physician confronted with a case of renal failure must ask himself at once if the underlying process is reversible A partial list of such disorders is included in Table 120 Once it has been ascertained that the renal defect is one of chronic irreversible extensive scarring the events leading to the production *of the* contracted or end stage kidney are mainly of academic interest

Table 120 REVERSIBLE RENAL DISEASE

Acute glomerulonephritis	Renal calcinosis
Acute tubular necrosis	Renal calculi
Acute cortical necrosis	Eclampsia
Acute pyelonephritis	Dehydration
Focal nephritis	Potassium depletion
Embolic nephritis	Congestion (due to heart *failure*)
Syphilitic nephritis	
Obstructive uropathy	

Relationship between Renal Disease and Hypertension Although *certain differences* of opinion exist the more prevalent point of view may be summarized as follows *It is clear* that disease of the kidney *may* induce hypertension This is excep

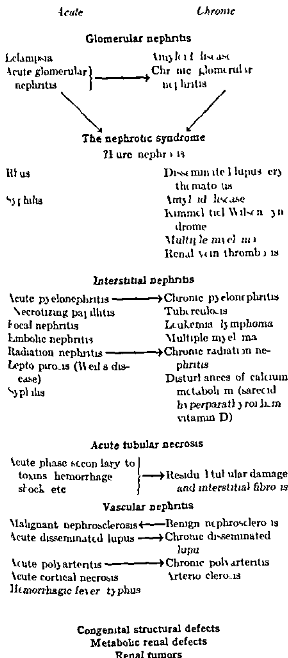
tional when the renal disease is unilateral but important for it may be amenable to surgical correction Commonly renal hypertension is due to bilateral disease of the kidneys In the author s view the majority of cases of hypertension appear to be primarily attributable not to renal disease but to multiple and as yet poorly defined factors involving the nervous system and the peripheral vasculature It is this form or this stage of the disease to which in our ignorance the term *essential hypertension* is applied Regardless of its cause however hypertension tends to induce disease in the small vessels in certain areas of the body and the renal arterioles and small arteries are particularly susceptible to such damage as a result of increased pressure It may be stated therefore that a large proportion of cases of advanced renal disease particularly in persons over the age of forty stems from hypertension but that most cases of hypertension are not due to primary renal disease Once the hypertensive patient has developed renal disease the latter may aggravate the hypertension which in turn may lead to further renal damage Thus the vicious circle proceeds To the relatively mild clinical picture in which the progress of the disease is slow the term *benign hypertension* is applied *Benign nephrosclerosis* therefore designates the pathologic and etiologic factor in the renal disease When on the other hand the progress of the disease is rapid with degeneration of the systemic and renal vasculature the condition is called *malignant hypertension* and the renal involvement *malignant nephrosclerosis* These terms refer to the rate of progression and to the degree of vascular damage rather than the underlying cause Hence either an individual with primary renal disease and secondary hypertension or an individual with primary hypertension and secondary renal involvement may develop malignant nephrosclerosis and malignant hypertension Some believe that the benign and malignant forms of hypertension represent fundamentally different diseases but the more prevalent view holds that they differ only in degree and rate of progression In general one may assume that the renal disease that occurs following years of elevated blood pressure during which urine examinations have been consistently negative represents extension of the disease process to produce vascular involvement of the kidney This is not a foolproof rule since occasionally renal biopsies in hypertensive patients with just such histories have revealed characteristic chronic interstitial pyelonephritis lending credence to the concept of some workers that most malignant hypertension is due to pyelonephritis

The Concept of Nephrosis Of the many concepts of renal disease that of nephrosis is perhaps the most confusing The word itself is etymologically nonspecific and is applied to a variety of clinical syndromes varied in etiology whose pathologic physiology is more of a generalized metabolic disturbance than that of a primary renal disease The configuration of abnormalities usually seen consists of massive proteinuria marked hypoproteinemia intractable edema and disturbances of lipid metabolism To such a picture the designation *nephrotic syndrome* has been applied and by reason of common usage will continue to be employed in this chapter The various points of view from which nephrosis is regarded and the etiologic factors involved will be discussed in Chap 232 It remains to add that another type of nephrosis *lower nephron nephrosis* has nothing in common with the syndrome discussed above and the term is probably incorrect anatomically Because of common usage however it must be mentioned in context with the more correct and descriptive phrase *acute tubular necrosis*

Renal Impairment and Renal Failure These have been discussed previously (Chap 19) A few of the more salient points may be summarized Diminished excretory capacity of the kidney (renal functional impairment) is characterized in its earlier stages by reduced ability of the kidney to perform standard tests of function The earlier type of impairment is recognized by diminished renal performance of standard tests such as the excretion of dyes maximal concentrating power and the clearance of urea These tests define the potential limits of renal performance but narrowing of these limits may still be compatible with ability to cope with ordinary daily functional demands When however the ability of the kidneys to clear the blood of *metabolites under usual conditions of load* is impaired the term *renal failure* may be applied This concept correctly stresses the fact that the characteristic manifestations of the two states as defined may be determined by the excretory load imposed upon the kidney Thus a high protein intake fever or thyrotoxicosis by increasing the solute load to be excreted may overtax the limited ability of the impaired kidney and cause renal impairment to merge into renal failure In addition the kidney has functions other than excretory such as its role in creatine metabolism and in the production of ammonia and perhaps of glucose These functions too may be impaired by renal failure

Classification of Renal Disease Any classification system for renal disease is necessarily made difficult by the overlapping of one set of criteria on another If for instance one chooses to follow the path of etiology the way may be complicated by the fact that a given microorganism may cause several types of renal disease all of which might be differentiated by a pathologic classification Similarly the morphologic concept suffers from the difficulty

Table 121 CLASSIFICATION OF BILATERAL RENAL DISEASE



Acute	*Chronic*
Glomerular nephritis	
Eclampsia	Amyloid disease
Acute glomerular nephritis →	Chronic glomerular nephritis
The nephrotic syndrome	
Pure nephrosis	
Rhus	Disseminated lupus erythematosus
Syphilis	Amyloid disease
	Kimmelstiel-Wilson syndrome
	Multiple myeloma
	Renal vein thrombosis
Interstitial nephritis	
Acute pyelonephritis →	Chronic pyelonephritis
Necrotizing papillitis	Tuberculosis
Focal nephritis	Leukemia lymphoma
Embolic nephritis	Multiple myeloma
Radiation nephritis →	Chronic radiation nephritis
Leptospirosis (Weil's disease)	Disturbances of calcium metabolism (sarcoid hyperparathyroidism vitamin D)
Syphilis	
Acute tubular necrosis	
Acute phase secondary to toxins hemorrhage shock etc →	Residual tubular damage *and interstitial fibrosis*
Vascular nephritis	
Malignant nephrosclerosis ←	Benign nephrosclerosis
Acute disseminated lupus →	Chronic disseminated *lupus*
Acute polyarteritis →	Chronic polyarteritis
Acute cortical necrosis	Arteriosclerosis
Hemorrhagic fever typhus	

Congenital structural defects
Metabolic renal defects
Renal tumors

In this table the *forms of the major divisions of* renal disease which tend to be acute are listed to the left in the above columns and the chronic forms to the right *The arrows indicate by their direction that acute lesions* may result in chronic disease or in the case of nephrosclerosis that an acceleration of the benign form may appear as acute disease The characteristic lesion of eclampsia is found in the glomerulus so that morphologically and clinically it resembles acute glomerular nephritis although it is etiologically dissimilar described early in the chapter that glomerulonephritis and nephrosclerosis may in late stages have many features in common The separation of acute and chronic renal disease forms a basis for a chronologic *system of classification which has important* prognostic advantage for the clinician Here again however in many forms of renal disease the dividing line between acute and chronic states may not be clear cut and may be described only by such unsatisfactory terms as "subacute" An arbitrary classification embodying all these concepts is presented *in Table 121 in order to orient the reader* to the discussion to follow rather than to introduce a completely adequate classification of renal disease *The nephrotic syndrome which would rest uncom*fortably in any single system of classification is afforded a position of its own in a clinical sense and acute tubular necrosis—a pathologic entity of varied etiology—is similarly treated

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John P Merrill

ACUTE GLOMERULONEPHRITIS

Acute diffuse glomerulonephritis occurs most frequently in childhood It is less common in adult life although well documented cases have occurred *for the first time in patients over sixty years of age* The true incidence of the disease is not known since milder cases often escape detection and this fact must be borne in mind by those who would consider the chronic form of the disease a separate etiologic entity Acute glomerulonephritis is most prevalent between the third and seventh year of life and occurs more commonly in males than in females Occasionally multiple cases of glomerulonephritis occur in families associated with congenital defects such as deafness Climate plays no such important role as it does with rheumatic fever for the incidence is approximately the same in the Northern and Southern United States

Etiology The most important etiologic factor appears to be renal hypersensitivity to extrarenal in*fection particularly of the upper respiratory tract* The commonest infecting organism is the group A beta hemolytic streptococcus of which type 12 and *perhaps type 4 appear to* be particular offenders Although acute nephritis has been reported in epidemics and in small population units such as the *family it is* generally considered a sporadic disease The extreme variability in attack rates for nephritis

following streptococcal infection when compared with the same rather constant relationship (3 per cent) for rheumatic fever suggests that there may be nephritogenic strains of streptococcus and indeed that even the type 12 organism may vary in its nephritogenic capacity Acute nephritis has also been reported to follow pneumococcal pneumonia subacute bacterial endocarditis and gastroenteritis due to the common enteric pathogens In contrast to rheumatic fever glomerulonephritis may follow deep streptococcal infections as well as those manifested by superficial pharyngitis Staphylococcal infections have occasionally been implicated In addition acute glomerulonephritis and the nephrotic syndrome have been reported following generalized reactions to poison oak and in relation to atopic dermatitis In some of these cases the relationship may be based upon the provision of a portal of entry for the streptococcus by the skin lesions Prolonged cold and exhaustion preceding some reported cases of the disease probably serve as factors predisposing to the streptococcal infection rather than as an independent agency The disease has also been reported in relation to other hypersensitivity states such as dermatitis due to an insect repellent after bee sting and in secondary syphilis

These observations suggest that the inflammatory process in acute glomerulonephritis is a manifestation of hypersensitivity to a bacterial product The correlation of the disease with streptococcal antibodies is not clear cut however since it may develop following streptococcal infections whose prompt treatment has prevented the development of circulating antibodies Serum complement is frequently low during the acute attack a fact which has been interpreted as a sopping up of complement at the site of antigen antibody combination The explosive onset of nephritis several weeks after bacterial infection as well as the shorter latent periods with acute exacerbations is in keeping with the concept of hypersensitivity In experimental animals lesions which closely resemble the human disease have been produced by nephrotoxic sera from heterologous species and identical lesions have been produced by the inoculation of homologous kidney extracts combined with streptococci The best working hypothesis is that modification of kidney protein by contact with the streptococcus produces an antigen to which antikidney antibodies are formed

Pathology Grossly the kidneys may appear normal or only slightly enlarged On removal of the capsule the surface may be found to be irregularly flecked with small hemorrhagic areas On microscopic section the fundamental glomerular involvement is revealed The glomeruli are diffusely involved and appear more cellular than usual owing to the proliferation and swelling of the endothelial cells of the tuft In addition polymorphonuclear leukocytes characteristic of the inflammatory process add to the appearance of cellularity Within the capsular space one may see exudate fibrin leukocytes and red blood cells which may also appear in various stages of degeneration further down in the tubules The tubules themselves in the early stage of the disease show little but the nonspecific change of cloudy swelling This may in part be due to disturbance in the supply of blood which comes by way of the narrow partially obstructed glomerulus There may be some edema of the interstitial tissue but early there is little involvement of the arterioles In all probability in those cases in which the disease is mild and followed by clinical cure the regression of these lesions is rapid with little residue save an occasional scarred glomerulus The lesions may however progress in characteristic fashion until the picture resembles that of the so called subacute stage Here the kidneys grossly appear slightly enlarged and there may be scattered deposits of lipid material

Microscopically the glomeruli may appear to be occluded by the mass of proliferated endothelial cells some of which show hyaline change The degree of irreversible occlusion may account for the other changes in the kidney as a result of interruption of the blood supply normally reaching them by way of the glomerulus The hallmark of this stage of the lesion is the epithelial crescent a proliferation of the capsular epithelium seen in various stages of development The tubules now may show marked degenerative changes with fatty degeneration necrosis and atrophy of the epithelium Scattered fibrotic changes begin to appear in the interstitial tissue setting the stage for the third or chronic phase This is marked by scarring which contributes the granular contracted appearance seen in the gross Glomerular changes have now progressed to hyalinization with almost complete destruction of the architecture and in many areas large sections of tubules have been replaced by fibrous tissue Others may show hypertrophic changes best seen when the entire nephron has been teased out The most striking architectural alteration however now appears in the small arteries which show thickening of the intima with marked narrowing or even obliteration of the lumen In this stage the vascular change has become a dominant factor and indeed the pathologic picture may be difficult to distinguish from so called nephrosclerosis

Pathologic Physiology In acute glomerulonephritis is seen one of the rare close correlations between structural change and disturbance of function The obstruction of the glomeruli by inflammatory change and endothelial proliferation would be expected to interfere with the normal filtration

process and indeed function studies in this stage show an excessive reduction in filtration rate and filtration fraction Lesser disturbances of functioning tubular mass are found when the measurements of T_m PAH and T_m glucose are made Renal blood flow is also reduced but to a lesser extent than filtration rate Clinically these changes may be manifest by a small volume of urine (impaired filtration) with a normal or elevated specific gravity (less impaired tubular function) The increased capillary permeability secondary to inflammation is reflected by the protein and red blood cells in the urine Because of the wide distribution of the edema it has been postulated that capillary permeability generally is increased and there is experimental evidence that capillaries other than the glomerulus may be involved There are other explanations for the edema however and the observation that the edema fluid of acute nephritis has the low protein characteristic of transudates would seem to contradict this view The early edema of acute nephritis is probably a function of decreased filtration of sodium plus continuing intake of sodium and water with a possible contribution from increased resorption of the sodium fraction reaching the distal tubules Although hypertension and congestive heart failure may play a role in the edema found later in the course of the disease they almost certainly do not do so in the earliest phases The heart does not appear to be consistently involved in the inflammatory process although changes resembling the Aschoff bodies of rheumatic fever have been found in the myocardium About one third of the patients hospitalized have moderate elevation of blood pressure and about 10 per cent may have severe hypertension This hypertension can be said to be truly renal in origin although ill advised attempts at fluid therapy may contribute to its severity When present edema is largely attributable to positive balances of sodium and it may be aggravated by the rapid onset of hypertension which together with the overhydration may result in frank cardiac decompensation as manifested by an enlarged heart and the classic signs of left ventricular failure Cerebral edema in turn may be aggravated by these factors although an element of vascular spasm has been postulated to account for the convulsive episodes which may occur This vascular spasm difficult as it is to demonstrate may be reflected along with the hypertension by the changes in the retinal vessels In acute glomerulonephritis sudden diureses occur which cannot be accounted for on the basis of slow healing of an inflammatory lesion this fact has been thought to reflect an element of relief of vasospasm and resumption of blood flow in the kidney

General Clinical Picture In mild cases symptoms may be absent and the signs limited to undetected proteinuria and microscopic hematuria In the classic severe case a streptococcus pharyngitis may be followed in 10 days or 2 weeks by the sudden appearance of general malaise headache costovertebral angle pain fever puffiness of the eyes circumoral pallor and the typical urinary findings Occasionally in the less observant patient the dyspnea of congestive heart failure may be the presenting symptom reflecting a somewhat later stage of the disease whose onset had been unnoticed except for vague malaise

Signs and Symptoms Physical examination in mild cases may reveal little except puffiness of the eyes The patient may have a slight elevation of temperature and some evidence of residual pharyngitis There may be some tenderness in the flanks or costovertebral angles and he may complain of vague generalized abdominal distress One third of the patients show an elevation of blood pressure when this is marked—particularly if the patient has been overhydrated—the signs of cardiac failure may supervene In such cases edema may be more marked and the heart may be enlarged to percussion There may be a rapid rate a gallop rhythm elevated venous pressure bilateral rales at the lung bases and pleural fluid The electrocardiogram may show evidence of left ventricular hypertrophy with nonspecific inversion of the T waves across the chest Severe hypertension is frequently accompanied by cerebral manifestations which may take the form of headache drowsiness and vomiting These may progress to muscular twitching and frank generalized convulsions followed by semicoma Blurring of vision commonly accompanies these attacks Although as a rule the eye grounds are normal in acute glomerulonephritis with marked elevation of blood pressure one may see hemorrhages exudate and constriction of the arteries Occasionally frank papilledema may accompany these changes

Examination of the Urine This may be the only method of positively making the diagnosis of acute glomerulonephritis The urinary findings vary from microscopic hematuria with traces of protein to grossly bloody urine or the coffee colored urine which represents the acid hematin residue of the red cells Frequently the urine may be described by the patient as dirty or smoky depending upon the number of red blood cells and the amount of acid hematin present Proteinuria may be the earliest sign and the last one to disappear Markedly concentrated urine may be elaborated in the early stages of the disease but the specific gravity may become normal or low as the renal lesion progresses Low urinary specific gravities also accompany the diuresis that may occur after a period of oliguria In this situation renal function may be good and the decrease in specific gravity the result of the loss of fluid

accumulated during the oliguric stage of the disease A finding pathognomonic of acute glomerulonephritis is the so called blood cast which consists of red blood cells enmeshed in fibrin and protein Hyaline and granular casts may also be present in the early stages of the disease with waxy and fatty casts occurring somewhat later The urine *volume is closely related to the severity of the disease* the greater diminution representing increased severity of the glomerular lesion Total anuria occurs in about 2 per cent of the hospitalized cases and 2 or even 4 days of anuria is not incompatible in children with complete recovery For periods longer than this particularly in the adult anuria in acute glomerulonephritis reflects a poor prognosis The characteristic pattern of renal functional disturbance has already been mentioned Aside from albuminuria and abnormalities in the sediment no disturbance of renal function may be evident by the usual clinical tests In general frank nitrogen retention is seen in the severe form of the disease associated with oliguria and hypertension Less than 5 per cent of the patients become severely uremic during the initial acute attack A normochromic normocytic anemia occurs in many patients with acute glomerulonephritis It may occur in the absence of nitrogen retention but is most marked *when the nonprotein nitrogen is elevated* Inhibition of the bone marrow as well as a hemolytic tendency in the disease accounts for this phenomenon Some degree of hemodilution due to overhydration may also contribute The white cell count is not markedly abnormal unless severe infection is present The degree of derangement of the blood chemical pattern depends upon the severity of the renal failure and the adequacy of therapy rather than upon the disease itself Characteristically during the acute attack the serum complement may be low and the antistreptolysin titer high Some decrease in serum protein levels may be apparent

Diagnosis The diagnosis of acute glomerulonephritis requires the findings of proteinuria and hematuria The blood cell cast is characteristic but may be absent in typical acute cases Changes in the hematologic picture and in the blood chemical pattern as well as the history and physical findings depend to a large extent upon the severity of the disease Other kinds of proteinuria such as orthostatic proteinuria must be considered as well as that which may result from a previously unnoticed subacute or chronic form of the disease Other causes of hematuria are renal tumors nephrolithiasis and bleeding lesions of the lower urinary tract Here the finding of blood casts which can be formed only in the nephron is of great help So called renal irritation may be seen following scarlet fever or during the course of other acute febrile illnesses and is accompanied by microscopic hematuria and proteinuria This cannot be considered acute glomerulonephritis Here time relationship to the original insult severity of the renal lesion and subsequent course may help to differentiate Disseminated lupus erythematosus and polyarteritis nodosa may cause renal lesions which are pathologically clinically and perhaps etiologically similar *and can be differentiated only by other systemic* manifestations of these diseases When an accurate history is not obtained acute tubular necrosis particularly that due to ingested or inhaled toxins such as carbon tetrachloride may faithfully mimic every aspect of acute glomerulonephritis

Clinical Course In the vast majority of children the clinical course is relatively benign and progresses to complete healing Less than 5 per cent of those afflicted die of the acute disease However the mortality is greater and the progression to the chronic state more frequent in adults than in children Death when it occurs is due to uremia congestive heart failure and hypertensive encephalopathy which is usually accompanied by convulsions These manifestations however may all occur in children who then have no evidence of the disease 1 year later

Prognosis There appears to be no relation between the severity of the disease and the prognosis *Indeed the impression is occasionally gained that* in children at least the severe acute forms of the disease are more frequently associated with a better prognosis The prognosis is markedly improved with decreasing age There appears to be no relation between the pattern or the severity of impairment of renal function and the eventual prognosis

Treatment There is no specific treatment for acute glomerulonephritis Bed rest in the early stages appears to be of prime importance Any evidence of residual infection in the pharynx or elsewhere should be promptly treated with the appropriate antibiotics ACTH and cortisone have not proved of value in acute glomerulonephritis and indeed because of their effect upon hypertension and protein catabolism are contraindicated Until the physician is certain about the volume of urine fluid protein and electrolytes should be restricted as indicated under Acute Renal Failure In the absence of nitrogen retention the protein intake should be low (0 5 Gm per kg of body weight) during the acute stage and nonprotein calorie intake as high as possible Although the evidence that a high protein intake is deleterious in acute renal disease in animals is conclusive this fact and the increase of osmotic work in excreting protein metabolites has not been demonstrated in man Nevertheless a moderate restriction of protein has a good basis in common sense under these conditions The anemia that may develop should be treated only when the hematocrit drops below

30 and then by the infusion of small amounts of packed fresh red blood cells because of the danger of suddenly increasing intravascular volume in patients with hypertension and congestive failure Congestive heart failure when it develops should be treated like any other instance of left ventricular failure with particular regard to restriction of fluid and sodium intake The treatment of hypertensive encephalopathy has been described previously on p 1331

The problem of when to begin activity following acute glomerulonephritis is a difficult one The urine should be examined two or three times a week *for protein red cells and casts The last may be* estimated and compared by the semiquantitative method of Addis When nothing but a small amount of protein remains or when a plateau appears to have been reached in improvement the patient may be allowed gradually to be up and about and the effect of mobilization may be followed by these techniques plus the sedimentation rate If there is a marked rise in the sedimentation rate or in the proteinuria or cylindruria bed rest should be resumed and a therapeutic test made again a week or 10 days later If after 3 or 4 months there is no evidence of improvement *the subacute stage has* been reached and treatment may be planned accordingly Every *effort must be made to prevent* recurrence or exacerbation Such measures include *the removal of infected tonsils and other foci of* infection Appropriate chemotherapy should accompany *such procedures Prolonged rest in the* hospital may not necessarily be of optimal value because of the danger of a cross infection Prophylactic sulfonamide or oral penicillin therapy in the subacute stage or for some months after the healing of an acute stage may be of value The potential hazard of sensitization makes the latter method preferable

The manifestations of *eclampsia* are similar to *those of acute glomerulonephritis* although they occur in a totally different setting The characteristic *renal lesion of eclampsia* is extreme narrowing of the glomerular capillary lumen with thickening of the capillary basement membrane and swelling of the glomerular epithelial cells surrounding the capillaries The clinical manifestations of the disease are described on p 1325

CHRONIC GLOMERULONEPHRITIS

Different opinions have been held as to whether chronic glomerulonephritis was a *separate etiologic* entity (type II nephritis) or the result of progressive changes following acute glomerulonephritis Advocates of the first point of view pointed to the frequent lack of evidence for antecedent acute nephritis and to the different pathologic pictures in the two conditions It is most probable however that chronic glomerulonephritis in which no history of an acute episode can be obtained is nevertheless the result of chronic changes following an unrecognized or subclinical attack of the acute disease In this view the pathologic changes in chronic glomerulonephritis represent chronic fibrotic change as a result of progression after an initial acute inflammatory response This view is supported by the fact that the clinical and pathologic picture of chronic glomerulonephritis may be identical whether or not an antecedent history of acute glomerulonephritis is obtained The clinical course may *be characterized by no more than minimal* proteinuria and microscopic hematuria until the symptoms of hypertensive disease or uremia occur Exacerbations may follow upper respiratory disease *or infections elsewhere in the body* or may be secondary to nonspecific trauma such as fatigue *and exposure to cold During such exacerbations* there may be a marked increase in urinary ab*normalities* with hypertension edema and nitrogen retention all of which may improve with bed rest *and treatment* Lacking a *previous history in such* instances it may be difficult to differentiate such *exacerbations from an initial attack* of acute glomerulonephritis The nephrotic syndrome may also *present as the initial manifestation of chronic* glomerulonephritis Renal amyloidosis may cause *chronic glomerular lesions whose clinical manifestations* except for a lesser incidence of hypertension *may simulate any stage of the more common form* of chronic glomerulonephritis

Treatment is confined to the elimination of those factors predisposing to exacerbations of the disease When hypertension or renal failure occurs the treatment is that of the particular complication The combination of hypertension and uremia carries a grave prognostic significance and mitigates against the lasting success of any known form of treatment *for hypertensive disease Patients with chronic* glomerulonephritis may also exhibit the signs of chronic pyelonephritis Low grade infection of this sort is difficult if not impossible to eradicate and the use of multiple antibiotics should be attempted with caution because of the danger of producing drug resistance Acute infection should be treated vigorously *to prevent further destruction* of renal parenchyma

THE NEPHROTIC SYNDROME

Muller in 1905 coined the word *nephrosis* to designate a disease state of the kidneys which was not characterized by *inflammation* and to which he deemed the suffix "itis" to be inappropriate As a descriptive term it represented degenerative disease of the tubules for according to Muller and many

since lesions of the glomerulus were frequently not demonstrable

An increasing amount of evidence indicates that the glomerulus is involved We know for instance that the nephrotic syndrome may be a part of the picture of chronic glomerulonephritis Studies of renal function in nephrosis frequently give evidence of impairment in filtration rate and suggest a pattern similar to that of chronic glomerulonephritis although the history and other findings of the disease may be minimal Amyloid disease of the kidney and intercapillary glomerulosclerosis are both represented by typical lesions in the glomerulus In both the picture of nephrosis may be present Other observers have stressed the lesion of the basement membrane of the glomerular capillary in nephrosis The restaining by new techniques of sections of kidney taken from so called pure nephrosis" has revealed lesions of the glomerular basement membrane previously not recognized For this reason and because the clinical picture of nephrosis may be present in disease states of apparently widely differing etiology the appellation *nephrotic syndrome* is perhaps more appropriate By this is implied the syndrome manifested by massive edema proteinuria hypoproteinemia and (usually) elevation of the serum cholesterol and lipids The fact that the glomerulus may be involved however helps only little in the fundamental understanding of the disturbance itself which remains one of the most complex and fascinating mysteries in medicine

Etiology The nephrotic syndrome may be one of the manifestations of such etiologically different renal diseases as chronic glomerulonephritis amyloid disease of the kidney syphilitic nephritis thrombosis of the renal vein and disseminated lupus erythematosus In children one may see the nephrotic syndrome unaccompanied by anamnestic physical or chemical evidence of any of these diseases The recovery rate among such children is high and in the past the disease would have been labeled pure nephrosis Whether such an entity exists or whether like acute glomerulonephritis in children it is a glomerular lesion which completely heals has not been settled Studies on animals suggest that urinary losses of protein may be the major contributing factor to the entire metabolic derangement

Pathology The pathologic lesion in the nephrotic syndrome depends upon whether the underlying problem is one of amyloid disease syphilis chronic glomerulonephritis or intercapillary glomerular sclerosis In pure nephrosis" the existence of the distinctive glomerular lesion was previously denied Whether in such cases special techniques will decisively demonstrate lesions of the basement membrane is yet uncertain All however agree that there may be degenerative changes in the tubular epithelium with scattered lipoid deposits which in polarized light appear doubly refractile

Pathologic Physiology The functional disturbances in the nephrotic syndrome may be roughly regarded from two points of view—disturbances in renal function and disturbances in fat and protein metabolism The renal component is characterized by excessive retention of sodium and marked proteinuria The best explanation for proteinuria is that these losses are entirely dependent on increased glomerular permeability The protein which appears in the urine is not qualitatively different from the plasma proteins of normal individuals The representation of each fraction however is quantitatively different from the normal The plasma protein disturbance is characterized by a marked hypoalbuminemia The total globulins are increased in the alpha and beta fractions and there is a decrease in the gamma globulins Serum cholesterol and total lipids are elevated and there is said to be a characteristic disturbance pattern in the lipoproteins Plasma amino acid levels tend to be low These latter factors all suggest some defect in liver function Histologically however no lesions are seen in the liver and the clinical tests of liver function show no disturbance It is possible though unproved in man that the renal losses of protein may account for the hypoproteinemia and that the accompanying abnormalities in lipid metabolism may be compensatory " In the full blown nephrotic syndrome however it is difficult by high protein feeding or the infusion of albumin to raise the levels of plasma protein more than transiently and to a minor degree Indeed both of these measures tend to increase proteinuria and the infusion of albumin may be followed by the elimination in the urine of 90 per cent of the infused protein

Hypoalbuminemia by decreasing the plasma oncotic pressure promotes edema as does the decreased tissue back pressure which must obtain in many of these protein depleted patients Transfer of fluid from the intravascular to the interstitial compartment tends to decrease plasma volume Recent evidence suggests that decreased plasma volume may increase aldosterone secretion thus accentuating sodium retention Increased urinary excretion of aldosterone has been found in nephrotic patients Diuresis however apparently may occur without gross changes in plasma volume or colloid osmotic pressure It is possible that the latter changes might not be noticed since a small increase in oncotic pressure would mobilize interstitial fluid which would then obscure the increase in serum protein Nevertheless it has been a frequent observation that improvement in the nephrotic syndrome whether spontaneous or induced by ACTH is accompanied by improvement in these parameters The role of the renal mechanism in edema

formation is likewise not clear Although a decreased filtration rate has been implicated in the formation of edema the filtration rate in the nephrotic syndrome may be reduced normal or even supernormal The renal tubules however tend to retain more of an infused sodium load than do those of normal persons and to excrete a nonresorbable anion with potassium rather than sodium This fact might suggest an adrenal cortical effect possibly that of aldosterone Adrenalectomy in fact has been reported to be followed by large sodium losses even with nitrogen retention and marked decrease in filtration rate

The lipidemia that occurs is striking with high levels of both free and esterified cholesterol and phospholipid fractions The plasma often appears milky Since in the experimental animal repeated plasmapheresis may cause a hypercholesterolemia the relationship of this to the hypoproteinemia might be considered an ineffectual attempt to increase oncotic pressure or as has been suggested increased lipid transport from fat depots to compensate for protein losses The frequent finding of a low basal metabolic rate suggests a reason for the hypercholesterolemia It is difficult however to assess the actual meaning of a low basal metabolic rate because of the difficulty of calculating surface area in the edematous patient There is evidence that thyroid function is normal and that the protein bound hormone may be lost in some quantity in the urine

Patterns of renal function vary with duration and degree of renal involvement There is a tendency however for the filtration fraction to be somewhat depressed

The profound metabolic changes which may be induced in the nephrotic syndrome by the administration of the adrenal steroids or ACTH may throw new light upon the pathologic physiology The diuresis which may occur during the course of treatment or follow its cessation results in massive losses of sodium and edema fluid in increased glomerular filtration rate (although diuresis may occur without increased filtration rate) decreased proteinuria increase in plasma protein and decrease in serum cholesterol Similar changes result from the so called "spontaneous diuresis" Such facts suggest that the glomerulus is a primary site of the disease but that the syndrome is characterized by reversible hemodynamic and metabolic processes early in the course Irreversible organic lesions in the nephron may be eventually superimposed upon the reversible changes

Signs and Symptoms The onset of the nephrotic syndrome depends in part upon etiology In children it may occur rather suddenly with the appearance of generalized edema days or weeks following upper respiratory infection or indeed without any antecedent infection at all In others the onset may be insidious with first dependent then generalized edema and the accumulation of fluid in the serous cavities In the patients with chronic glomerulonephritis or intercapillary glomerulosclerosis (*Kimmelstiel Wilson s syndrome*) the onset may masquerade as or be masked by congestive heart failure Pallor is often a striking feature The generalized edema may be accompanied by anorexia and other gastrointestinal disturbances Marked ascites may be present as well as hydrothorax and both contribute to respiratory embarrassment The skin of the abdomen thighs and lower legs is tense and shiny and may develop splits from which serous fluid may leak or which may act as portals of entry for infection The urine volume is usually scanty with a high specific gravity There is marked proteinuria, with many hyaline casts occasional granular casts and rare red blood cells There may be a slight anemia which becomes more severe with the onset of renal failure The disturbances in plasma protein and lipids have been described Nitrogen retention may occur as the disease progresses to more diffuse involvement of the kidneys The erythrocyte sedimentation rate is characteristically high but this is probably a factor of the lipemia and high globulin rather than evidence of infection Blood pressure is usually normal until the onset of renal functional impairment

Clinical Course The disease may be characterized by spontaneous remissions during which diureses occur and the metabolic abnormalities diminish Over a period of years particularly in children such waxing and waning of the disease picture may be followed by permanent cure In adults however although the disease is not common it frequently terminates in uremia hypertension and heart failure if untreated It is not unusual to see such patients lose their edema with the onset of uremia and severe hypertension Patients with the nephrotic syndrome are unusually susceptible to infections of all types possibly because of a low plasma gamma globulin The pneumococcus and streptococcus are common offenders particularly in the form of pneumococcal pneumonia and peritonitis and were a frequent cause of death before the era of antibiotics A frequent complication is the onset of tender red areas resembling erysipelas on the anterior thighs and abdomen which may be accompanied by fever vomiting and general signs of toxicity Occasionally the abdominal signs may include severe pain generalized tenderness and rigidity and closely simulate acute intraabdominal conditions requiring surgery Such episodes have been termed *the nephrotic crisis* Following such attacks it is not unusual to see a spontaneous diuresis and remission

A drop in plasma amino acids may precede such crises.

Prognosis. About 50 per cent of children with the nephrotic syndrome recover without apparent sequelae. Some of these may have shown signs of renal failure during part of the course of their disease. The remainder, however, go on to chronic glomerulonephritis with its sequelae. The prognosis of the nephrotic syndrome with amyloid disease and Kimmelstiel-Wilson's syndrome is that of the underlying disease process. Syphilitic nephrosis is a curable type of nephrotic syndrome. The onset of hypertension or nitrogen retention in the patient with nephrotic syndrome is an ominous prognostic sign.

The majority of adults show the progression to chronic nephritis. The effect of the adrenal steroids and ACTH upon the ultimate course of the nephrotic syndrome awaits fuller evaluation. We cannot be sure that the striking remissions induced are cures, but there is some slight evidence that a larger percentage of those treated may go on toward permanent healing.

Treatment. This should consist of a diet low in sodium and high in potassium but without drastic salt restriction. The protein intake should be normal, but forced feeding of protein is not apparently of value. Care should be taken to prevent splitting of the tense skin and to avoid infection if this occurs. Prompt treatment with appropriate antibiotics is indicated for the attacks of cellulitis and similar infections. Mercurial diuretics combined with xanthines may be tried for the treatment of edema. Frequently these are ineffective, however, and if so should not be continued in an effort to achieve diuresis with larger doses than those normally employed. Mercurial diuretics should never be used intravenously. It is important, however, to see that proper absorption of the drug occurs from a nonedematous site. The use of cation exchange resins has apparently not been effective, nor is the diuretic effect of the administration of urea worth the distress it causes. Salt-poor concentrated human serum albumin is effective but is prohibitively expensive; its effect is transient, and a large percentage of it is lost in the urinary protein. A transient sodium and water diuresis may follow the infusion of plasma substitutes of high molecular weight such as gelatin, dextran (12 per cent). Until the metabolic handling of dextran is further delineated, however, repeated infusions of large amounts of this substance for the treatment of nephrotic edema cannot be advocated. The use of ACTH may result in a diuresis either during the course of therapy or immediately upon cessation. This occurs in 70 per cent of cases uncomplicated by renal failure in the first or second trials. The diuresis is often accompanied by the metabolic improvement mentioned above. ACTH may be used in the average adult in dosages of 150 to 250 mg a day, given in divided doses intramuscularly. The long-acting ACTH gel preparation may be used in 100 mg daily. Most effective is the continuous intravenous infusion of as little as 25 mg ACTH in 5 per cent glucose and water over a period of 12 hr or longer. Similar results may be obtained by the oral administration of 300 to 400 mg per day of cortisone or hydrocortisone in divided doses. Meticorten (prednisone) in oral doses of 100 to 125 mg per day is equally effective. The physician should be familiar with the complications of steroid therapy which are described elsewhere (p. 585). The treatment should be continued for a 2-week period unless diuresis occurs earlier. Not infrequently, a second or third course will induce diuresis where previous therapy has failed. During the initial days of therapy, the patient may gain weight because of increased sodium retention. This may be minimized in some cases by the use of mercurial diuretics or carbonic anhydrase inhibitors (Diamox). Proteinuria may actually increase in the early part of the program and there may be transient episodes of hypertension. Diuresis may commence on the fifth to seventh day of therapy, or it may not appear until after the drug has been stopped. In the latter instance, the only beneficial result may be the loss of edema, whereas in the former all the metabolic abnormalities may be reversed. Disappearance of proteinuria heralds the most favorable result. The use of maintenance steroid therapy following a continuous course appears well worth while. The drug is given for 4 days a week only, which minimizes the manifestations of hypercorticism. Where proteinuria has disappeared with therapy and maintenance treatment been given, the number of long-term remissions (2 to 3 years) suggests the possibility of "cure." Nevertheless, there is inadequate evidence to ascertain whether after such a period the drug may be stopped without danger of remission. During therapy, supplemental potassium salts in the form of acetate or citrate yielding 20 to 30 mM of potassium per day should be given. Not infrequently, a poor result may be converted into a satisfactory diuresis by the infusion of 12 per cent dextran or of serum albumin 24 to 36 hr following the withdrawal of steroid treatment. ACTH or corticoid therapy is contraindicated in the presence of marked renal failure or hypertension. The induction of measles in nonimmune individuals has resulted in spontaneous diuresis. Treatment of the nephrotic syndrome with typhoid vaccine and with nitrogen mustards has been reported with questionable success. Induced malaria has also produced remissions.

Intercapillary Glomerulosclerosis (Kimmelstiel-Wilson's Syndrome). Approximately 60 per cent

of diabetics of long duration may show the lesion of intercapillary glomerulosclerosis and of these some 5 to 7 per cent may be associated with varying degrees of the nephrotic syndrome Characteristically this form of the nephrotic syndrome occurs in the sixth to seventh decade of life but it may be seen as early as age sixteen It is usually associated with a mild form of diabetes and with hypertension It is well correlated with arteriosclerotic changes elsewhere in the body and particularly with diabetic retinopathy Pathologically the characteristic lesion is a spherical deeply staining acidophilic mass of hyaline material occupying the center of a glomerular tuft Associated arterio- and arteriolonephrosclerosis is a constant finding along with some degree of interstitial and focal fibrosis and tubular atrophy and dilatation The etiology is unknown although experimentation implicates an adrenal cortical factor The administration of cortisone to rabbits made diabetic with alloxan may produce strikingly similar lesions The clinical picture is that of a mild nephrotic syndrome usually accompanied by hypertension and moderate vascular lesions The renal functional pattern shows nonspecific impairment similar to that of chronic glomerulonephritis With the use of polarized light one may find in the urine sediment doubly refractile lipoid bodies with the appearance of bright achromatic Maltese crosses" This is said to be characteristic The prognosis and clinical course are usually determined by the extent of the vascular disease rather than the renal lesions although an occasional patient dies in uremia Treatment is that of the diabetes of the hypertension and vascular disease and of the edema Adrenal steroid therapy should not be employed in such patients

Rarer Forms of Nephrotic Syndrome

Amyloid Renal Disease Involvement of the kidney by amyloid disease may produce the full blown nephrotic syndrome This is common with the secondary type but rare with the primary type of amyloidosis (p 720) Histologically the typical renal lesion is scattered amyloid deposits in the glomerular tuft The disease should be suspected in a patient with enlargement of the liver or spleen presenting the characteristic stigmata of the nephrotic syndrome Classically a previous history of chronic infection is elicited The renal lesion may progress to uremia although hypertension is the exception rather than the rule The diagnosis is confirmed by the demonstration of a positive Congo red test (Chap 91) It should be remembered in this test that a certain amount of the dye may be lost by binding to urinary protein The therapeutic problems are similar to those of the other forms of nephrosis and of uremia when the latter develops

Syphilitic Nephrosis This is a rare disease but important because it is amenable to specific antiluetic therapy The diagnostic points are the presence of the nephrotic syndrome usually of sudden onset in the face of positive evidence by history physical examination and serologic tests of the presence of secondary syphilis Antiluetic therapy is usually dramatic

Renal Vein Thrombosis This is an unusual but well documented cause of nephrosis A history of thrombosis elsewhere and evidence of anastomotic circulation may make the diagnosis

Multiple Myeloma This disorder may produce a typical nephrotic picture associated with myelomatous infiltration of the kidneys renal amyloidosis or both

INTERSTITIAL NEPHRITIS

In this discussion the term *interstitial nephritis* will be used to denote an exudative inflammatory response in the interstitial tissue of the kidney The term *pyelonephritis* for purposes of clarity denotes interstitial inflammation in both the parenchyma of the kidney and the renal pelvis while *pyelitis* signifies the involvement of the renal pelvis alone without spread to the renal parenchyma—a situation which is unusual in infections of any duration The changes of chronic interstitial nephritis usually secondary to pyelonephritis are the most frequent cause of chronic kidney disease in dogs and in man

Pyelonephritis Infection of the renal parenchyma is probably the commonest cause of hypertension and of uremia in women under the age of fifty and is an occasional cause in men The active phase of this disorder may be of the acute type with fever pyuria and bacteriuria or of the cryptic variety with lassitude and positive urine cultures as the principal features Under these circumstances the chief problems are those of identifying and eradicating the infectious agent and these have been discussed in Chap 144 which also includes a consideration of cystitis

In the terminal phase of chronic pyelonephritis all clinical and bacteriologic evidence of infection may be lacking the picture of hypertension uremia and vascular retinopathy may be indistinguishable from that produced by chronic glomerulonephritis or nephrosclerosis Indeed the three disorders or any two of them frequently coexist Occasionally it is possible to demonstrate by x ray that one kidney is much smaller than the other and such asymmetry is strong evidence that pyelonephritis is the primary disease process The recognition of pyelonephritis is usually easy if the patient is followed throughout the course of the disease but is frequently impossible if the subject is not ob

served until the terminal phase of contracted kidney with uremia has appeared

The treatment of pyelonephritis involves three problems (1) eradication of the infection (p 969) (2) management of hypertension (p 1327) and (3) the treatment of acute or chronic uremia as discussed on pp 1367 and 1366

Rarer Forms of Interstitial Nephritis

An acute diffuse interstitial nephritis has been described in association with such infectious diseases as diphtheria scarlet fever and Weil s disease Microscopically one sees an occasional focal but usually diffuse infiltration of the interstitial tissue by plasma cells lymphocytes and polymorphonuclear leukocytes In man such involvement is thought to heal without permanent damage Chronic interstitial nephritis in which similar pathology has progressed to degeneration and atrophy and fibrosis of renal tissue may also be seen Such lesions may follow the chronic infiltration with leukemia cells or the cells of multiple myeloma

The kidneys and renal pelves may be involved by suppurative processes as the result of (1) organisms reaching the interstitial tissues by way of the blood stream or (2) ascending infection from the lower urinary tract either by way of the ureters themselves or of the periureteral lymphatics When the kidney alone is involved by blood borne infections the condition of *focal* or *embolic* suppurative interstitial nephritis obtains This is frequently the result of staphylococcal infection blood borne from suppurative processes elsewhere in the body In bacterial endocarditis septic emboli to the kidney may result in a focal process which is frequently also accompanied by changes resembling those of acute glomerulonephritis Occasionally colon bacilli are found although the colon bacillus appears to be a rare causative agent in this type of nephritis Microscopically multiple small purulent foci are seen which may coalesce to form a larger *renal carbuncle* Occasionally the spread of such an infection to the perinephric tissues results in the formation of a perinephric abscess Here local tenderness or swelling in the costovertebral angle with pain on motion of the trunk (evidence of psoas muscle irritation) may give a clue to the diagnosis

A syndrome has been described following deep radiation to the renal areas which resembles those of acute nephritis and may progress to a picture similar to the chronic stage Changes begin 6 to 12 months after cessation of therapy with proteinuria but no hematuria There are a few such cases that go on to hypertension and azotemia and die in uremia Microscopically one notes a generalized intertubular fibrosis and in the later stages hyaline obliteration of the glomeruli with fibrinoid necrotic lesions of arterioles

Syphilitic Nephritis In less than 1 per cent of the cases of secondary syphilis poorly defined renal lesions occur represented by interstitial accumulation of mononuclear cells and lymphocytes which may encroach upon the tubules The clinical picture may vary from mild proteinuria alone to severe proteinuria and cylindruria with generalized edema and many of the characteristics of the nephrotic syndrome Renal function studies suggest the pattern seen in acute glomerulonephritis All of the abnormal phenomena may be reversed by appropriate penicillin therapy Interstitial lesions are characteristic of the Metabolic Renal Disorders discussed below principally those concerned with disorders of calcium and uric acid metabolism

VASCULAR NEPHRITIS

The term *vascular nephritis* includes several disorders in which the prime etiologic factor is disease of the renal vasculature This in turn usually reflects disease of the systemic vessels

Nephrosclerosis

The characteristic lesion of renal vascular disease is sclerosis of the arterioles manifested particularly by hyaline thickening of the intima of the afferent arteriole of the glomerulus This may be seen in other types of renal disease Indeed its end result —the scarred contracted kidney—is extremely difficult to differentiate from the final stage of chronic pyelonephritis or glomerulonephritis In the benign or slowly progressive form of essential hypertension this intimal thickening results in sclerosis of the arterioles and the resultant narrowing of the lumen compromises the blood supply to the areas supplied This leads to a patchy fibrosis with areas of normal tissue between Characteristically one sees a spotty thickening of the basement membrane of the glomerulus and finally obliteration of the capillary tuft Further tubular destruction and fibrosis result with renal function compromised according to the extent of the damage The end result of the fibrous changes is a contracted scarred kidney These renal vascular changes however do not necessarily reflect vascular changes elsewhere in the body In the malignant phase of *essential* hypertension the characteristic changes are a rapidly progressing endarteritis obliterans with marked thickening (onionskin) of the intima of the arterioles and necrosis of both the media and the intima If the onset is sudden and the progress rapid enough death may ensue before the fibrotic changes decrease the size of the kidney The pathologist then sees a normal sized kidney with the microscopic changes previously described and with its surface in the gross studded with punctate hemorrhages which resemble the embolic flea bitten

appearance Between the extremes of the benign and malignant changes one may see many varieties of structural change including the characteristic lesions of other renal diseases which may result in systemic hypertension Here the vascular lesion probably represents the result of hypertension rather than the underlying disease process

The signs and symptoms are those of hypertension and renal failure There are no specific urinary findings except occasional hematuria, the so-called "renal epistaxis" *The functional change early in hypertension is characteristically an increased filtration fraction, possibly representing constriction of the efferent arteriole* The treatment of nephrosclerosis is the treatment of hypertension and the accompanying renal failure when present The relationship between hypertension and vascular disease of the kidney has already been discussed in some detail (p 13_6)

Renal Arteriosclerosis

In renal arteriosclerosis the larger arteries are involved and this fact probably accounts for the moderate degree of depression of renal function frequently seen in elderly patients without specific disease In the absence of other forms of involvement it is rarely severe enough to cause frank renal failure

Rarer Forms of Vascular Nephritis

The renal lesion of disseminated lupus erythematosus is predominantly proliferation of the endothelium of the glomeruli Thickening of the basement membrane in an irregular fashion results *in the so-called hyaline "wire loop" lesion This* however may frequently be absent in the diseased kidney The early clinical signs and symptoms are predominantly those of the systemic manifestation of the disease Occasionally the nephrotic syndrome may appear Frequently there is marked proteinuria and the urine sediment may yield representatives of all forms of casts a *situation thought by* some to be typical of the disease but not consistently reliable Treatment with ACTH and cortisone which may markedly improve systemic manifestations only rarely helps the renal lesion and occasionally appears to hasten its progress The amelioration of systemic manifestations with adrenal *steroid and antibiotic therapy has resulted in a* marked increase in the number of cases dying in renal failure since this component proceeds unabated At necropsy such treated cases show lesions strikingly resembling those of chronic glomerulonephritis The renal lesions of polyarteritis nodosa resemble those of malignant nephrosclerosis except that there *is more perivascular cellular response* The effect of treatment with adrenal steroids is similar to that seen in lupus

The renal *manifestations of hemorrhagic fever* which were studied at length during the Korean conflict, are those of a generalized vascular disease whose etiology is yet unknown but which is probably infectious in nature Renal functional impairment, when it occurs may be mild and transient or may include prolonged oliguria and uremia The shock phase of the disease undoubtedly contributes to the renal lesion Microscopically the predominant changes are engorgement of blood vessels and *evidence of escape of blood into surrounding tissues* The vascular lesions of typhus fever may involve the kidney with resultant proteinuria and cylindruria which rarely progresses to renal failure

Platelet thrombi in thrombotic thrombocytopenic disease may involve the renal vessels and result in renal failure Occasionally such a case responds temporarily to steroid therapy

Bilateral symmetric cortical necrosis of the kidneys most frequently occurs in pregnancy usually in the setting of preeclampsia. The pathologic lesion *is necrosis of the cortices of both kidneys* occasionally complete but sometimes with wedge shaped areas of intact tissue separating the infarcted tissue The microscopic pathology is characterized by thrombosis of all small arteries and arterioles within the involved portion of the cortex. Although it has *been thought that this syndrome* was *100 per cent* fatal, it is probable that bilateral cortical necrosis is a severe manifestation of vasospasm which in other instances may yield only acute tubular necrosis and that the syndrome is compatible with clinical recovery

CONGENITAL STRUCTURAL DEFECTS

Polycystic Disease of the Kidney This condition is thought to result from embryologic failure of the union of the collecting ducts and the convoluted tubules It is manifested by multiple cysts some of which may be grapefruit size in both kidneys *The growth of these cysts is the result of increase* in size of individual cysts rather than the development of new cyst structures Their growth causes destruction of adjacent normal renal tissue with resulting fibrosis There is a strong familial tendency in polycystic diseases and there may be other cystic abnormalities in the liver and pancreas *Small ("berry") aneurysms of the cerebral vessels* may also occur Although the disease may result in death in childhood, characteristically the patient may do well until the fourth or fifth decades then the first clue to the diagnosis may be the signs and symptoms of hypertension, which occurs in about half the cases or renal failure The striking tolerance *of such patients to* marked renal failure and the length of survival with minute amounts of functioning renal tissue give an important commentary upon

served until the terminal phase of contracted kidney with uremia has appeared

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saturated urinary salts is an important etiologic concept Of recent interest is the fact that drugs tending to decrease urinary citrate excretion such as Diamox may play a role in the etiology of renal calcium calculi Hypercalcuria with or without hypercalcemia is an all important factor and must be carefully investigated The common causes for hypercalcuria are prolonged bed rest particularly in the postmenopausal stage metastatic bone tumors multiple myeloma Cushing s disease sarcoidosis vitamin D intoxication excess intake of calcium and phosphate (particularly as dairy products) hyperparathyroidism (5 per cent of urinary calculi are associated with parathyroid disease) acidosis and idiopathic hypercalcuria The latter condition appears predominantly in male patients The serum calcium and phosphate are normal

Diagnosis Patients with renal calculi may not infrequently be asymptomatic Renal calculi should be looked for in any of the above disease states Occasionally hematuria alone will be a manifestation Classically the passage of a renal stone down the ureter results in severe colicky pain radiating to the groin flank and testis and accompanied by the passage of clots and gross or microscopic blood Large staghorn" calculi may be asymptomatic except for vague costovertebral angle pain and the symptoms of obstruction and infection of the kidney The calcium containing stones and the mixed stones are radiopaque as is the cystine stone Uric acid stones are not The latter do not necessarily occur in patients with clinical gout and appear to be more frequent in patients of Jewish and Italian origins Evidence of osteomalacia or osteoporosis by x ray should lead to investigation for renal calculi In patients with normal renal function the Sulkowitch test performed on a casual urine specimen may indicate hypercalcuria This however should be checked by analysis of 24 hour urine specimens after several days of a 200 mg calcium diet Cystinuria may be indicated by the nitroprusside test but paper chromatography is perhaps essential Crystals of uric acid phosphate and cystine may be identified in dried urine specimens but with the exception of the latter they may not necessarily have significance for the etiology of the renal calculus The pH of a fresh urine specimen may give some clue as to the etiology of the stone since characteristically uric acid stones occur in acid urine and the mixed calcium stones in alkaline urines Where it can be obtained of course crystallographic analysis of the stone itself is conclusive and occasionally such a technique may reveal the presence of an artefactual inclusion of a psychoneurotic or malingerer

Therapy The general principles of the treatment of renal calculi are to treat the underlying disease particularly that causing hypercalcuria It is important to eliminate stasis and infection by appropriate means The urine volume should be maintained high to decrease the concentration of precipitable materials The injection of hyaluronidase to increase the excretion of urinary protective colloids which may decrease the formation of concretions has been advocated The use of this substance is of questionable value The ingestion of substances such as aspirin which are conjugated as glucuronides and excreted as such is apparently of some value Glucuronides significantly increase the solubility of calcium phosphate

In addition to the general measures patients with calcium stones should be placed on a diet low in calcium and phosphate The ingestion of aluminum hydroxide gels decreases the excretion of phosphate although it may result in an initial increase in calcium excretion Immobilized patients should receive physiotherapy to decrease mobilization of calcium from bony structures The use of mild acidifying agents to maintain a low urinary pH is of value However systemic acidosis may increase calcium mobilization if therapy is too vigorous There is no evidence that ingestion of foods high in oxalate increases the incidence of calcium oxalate stones Magnesium ammonium phosphate stones (triple phosphate) should be treated with mild acidifying agents aluminum hydroxide gels and appropriate antibiotics to discourage urea splitting infections Possibly a low protein diet to decrease urinary urea may be of value If there is no other contraindication patients with uric acid and cystine stones should be treated with mild alkali (sodium citrate) to increase the solubility of these substances in the urine

TUMORS OF THE KIDNEY AND BLADDER

With the exception of benign cysts and a rare large adenoma tumors of the kidney must be regarded as malignant Because of the late appearance of symptoms and signs of sufficient magnitude to lead to investigation and accurate detection the mortality in this disease is high Renal cell carcinoma is the most frequent tumor of the kidney appearing predominantly in the fourth to the seventh decade Early invasion of the small veins and the renal vein gives rise to metastatic spread to the liver lungs and bone Occasionally invasion of the left renal vein with obstruction of the spermatic vein may result in a varicocele Renal cell carcinomas may produce alkaline phosphatase so that the serum concentration may be elevated enough to be of diagnostic importance In children embryomas of the kidney are of importance These tumors are relatively undifferentiated and metastasize early by way of the small blood vessels Papillary carcinomas of the transitional epithelium of the

the adequacy of adaptive mechanisms in the face of very slowly progressing uremia There is nothing characteristic about the urinary findings except intermittent bouts of hematuria which may occasionally lead to massive hemorrhages into these cysts Typically large firm lobulated masses are palpable in the flanks Before the onset of renal failure the intravenous pyelogram may give a characteristic picture Surgical puncture and drainage of the cyst results in temporary relief of pressure phenomena but is of little long term benefit The treatment is that of the resulting hypertensive disease and uremia and of the frequent infection

Unilateral Renal Agenesis This is found in about 0 1 per cent of routine autopsies It is more frequent in males the left kidney is more frequently absent with hypertrophy of the opposite kidney which may be involved in an abnormality predisposing to pyelonephritis Possible absence of the contralateral kidney should always be considered when advocating unilateral nephrectomy *Hypogenesis* of one kidney is slightly more frequent and may result in a small functionless kidney frequently with pyelonephritic change The joining of two kidneys by a fibrous band or a band of renal tissue (*horseshoe kidney*) occurs occasionally and is without clinical significance except for the predisposition to pyelonephritis Duplication of the ureters or a double renal pelvis is of clinical importance only for the same reason Aberrant renal vessels rarely cause difficulty unless they cause obstruction to the urinary outflow tract or to the renal blood supply A congenitally *ectopic kidney* may be present in the true pelvis or in the iliac fossa connected to the bladder by an extremely short ureter It may give little difficulty except during pregnancy although again such abnormalities predispose to retrograde infection *Abnormal mobility of the kidney* may result in *nephroptosis* The ureter is of normal length although the kidney itself may be found just above the pelvis Congenital defects in body habitus lack of normal renal supporting structures postural defects and the stress of constant muscular straining or coughing may all contribute to nephroptosis Frequently there are no symptoms and those which do occur are usually due to interference with drainage of the ureter or to the blood supply giving rise to colicky pain (*Dietl's crisis*) Therapy is directed at supporting the organ externally and correcting the postural defects Surgical procedures are indicated only when it can be proved that the symptoms are the result of the malposition of the kidney

METABOLIC RENAL DISORDERS

Generalized Renal Calcinosis This may occur with or without stone formation is the result of disturbances of calcium and phosphorus metabolism (Chap 74) Among the specific etiologic factors are hyperparathyroidism hypervitaminosis D and excess calcium and/or alkali ingestion particularly in the presence of previous pyelonephritis These changes may progress to renal failure and death and the recognition of these conditions is important because at least in the early stages they are potentially reversible by appropriate therapy High serum calcium levels in uremia should lead the physician to investigate one of the above possibilities or alternatively those of myeloma kidney or sarcoidosis

The renal lesion and impairment of function arise from deposition of calcium in the renal interstitium with resultant fibrosis Occasionally renal calcinosis may be revealed by x ray although marked impairment may exist without x ray evidence of calcification Indeed it is probable that factors other than calcium deposition per se are operative The presence of band keratopathy is confirmatory evidence of hypercalcemia of long standing and its presence in renal failure suggests primary metabolic disease rather than hyperparathyroidism secondary to renal failure Renal disease secondary to systemic sarcoidosis results not only from involvement of the kidney by the granulomata but also by lesions similar to those of hypervitaminosis D Adrenal steroid therapy may result in some improvement Renal calculi have been seen in sarcoidosis

Gouty nephritis with renal failure may result from the interstitial deposition of urate crystals and patchy fibrosis The effect in diminishing such deposits by the long term use of uricosuric agents has not been properly evaluated The vascular component in gouty nephritis bears equal weight with the interstitial element

Myxedema This may be accompanied by abnormalities of renal dynamics and diminution of tubular maximal excretory and resorptive capacity Inborn errors of metabolism localized in the renal tubule and elsewhere may give rise to abnormal urinary constituents which in some instances may be reflected by disturbances of body fluid constituents These are discussed in more detail in Chaps 48 and 49

Diagnosis and Treatment of Nephrolithiasis A discussion of the mechanism of stone formation has been given in Chap 19 Of the clinically important types of renal calculi calcium phosphate stones comprise approximately 51 per cent calcium oxalate 13 per cent magnesium ammonium phosphate 20 per cent cystine 1 per cent and uric acid 6 per cent It should be remembered that frequently these stones are mixed The role of urinary tract infection and stasis cannot be too strongly stressed as an etiologic agent in stone formation The presence of a nidus for the precipitation of the super-

cortical necrosis In this latter syndrome the afferent arteriole and glomeruli may be involved as well In the experimental production of these lesions and in the pathologic picture there is evidence for the operation of a shunt of blood from the cortex through the medulla by way of the juxtamedullary glomeruli as suggested by earlier work Since however severe specific nephrotoxic insults are usually accompanied by circulatory disturbances the lesion here may be mixed and the common denominator may be ischemia Interstitial edema and loss of the tubular basement membrane were seen in both types of lesions The random regeneration of proliferating epithelial sheets as well as the persistent disruption of the tubular wall suggests that function in the nephrons may be permanently destroyed Although recurrent intravascular hemolysis with hemoglobinuria has been proved to cause a diffuse fibrotic process in the kidneys the relation of the heme pigment cast per se to the tubular damage is put in doubt by the lack of relation between tubular damage and the proximity of the pigment cast

Differential Diagnosis The first question to be asked by the physician confronted by acute renal failure is Is the process immediately reversible? (Chap 231) One must consider the possibility of obstruction of shock and severe dehydration On the other hand poorly documented chronic disease may frequently present as acute renal failure Here the size of the kidneys by x ray may be a valuable differential point A plain film of the abdomen (not an intravenous pyelogram) should be made Occasionally bilateral emboli to the renal vessels may be involved Renal failure resulting from circulatory disturbances or disorders of fluid balance have been termed *prerenal* or *extrarenal* uremia The dividing line between prerenal disturbances and intrinsic renal disease is not clear-cut however and the former if prolonged may result in diffuse parenchymal lesions

Clinical Course The primary manifestation of acute renal failure is suppression of the urine volume Less acute processes may occasionally impair the ability to excrete solutes without markedly decreasing volume but this is rare The duration of suppression may be a matter of 24 hr or as long as 6 weeks after which urine volume may increase Intermittent oliguria and polyuria strongly suggest obstructive uropathy not disease of the renal parenchyma

Oliguric Phase Total anuria for periods of more than 2 to 3 days is rare in acute renal failure When it does occur one should suspect acute glomerulonephritis or obstruction of the urinary tract More common is severe oliguria of 20 to 200 ml per day If the urine is poorly concentrated and there is a large load of metabolite to be excreted 400 to 500 ml per day may also represent acute renal failure The urine may be grossly bloody during the first few days of oliguria and show a typical dark red or brown color if hemolysis has occurred Proteinuria may be marked in the beginning and tends to clear After the first 2 days the urine specific gravity drops to 1 010 or below Small numbers of granular casts or heme pigment casts are seen as the oliguria continues Decreasing numbers of erythrocytes and increasing pyuria are seen although hematuria may persist as a result of irritation from a urethral catheter If acute renal failure has been precipitated by an acute traumatic episode as is frequently the case the serum nonprotein nitrogen mounts rapidly at first and less rapidly as oliguria continues This is markedly influenced by factors affecting protein catabolism Serum sodium and chloride concentrations tend to drop blood bicarbonate decreases as acid metabolites accumulate Serum potassium may be elevated and occasionally this rise is acute and marked Serum calcium tends to be depressed All of these values are markedly modified by the form of therapy and the factors increasing the catabolism of protein A normochromic and normocytic anemia frequently becomes manifest and the blood leukocyte count may rise as high as 25 000 even in the absence of obvious infection With progressive nitrogen retention nausea and vomiting appear marked abdominal distention may be troublesome and in prolonged oliguria diarrhea occasionally with bloody stools may occur The neuromuscular symptoms are those previously described for the general picture of uremia (p 161) and include somnolence disorientation twitching and convulsions Elevation of the diastolic blood pressure (100 mm Hg or more) occurs in 65 per cent of the cases and may be severe Retinal changes are infrequent although marked alterations including separation of the retina have been seen in acute renal failure accompanying eclampsia Congestive heart failure and acute pulmonary edema are dreaded and not infrequent complications the incidence depending to some extent upon the severity of the hypertension and the zeal with which fluid is administered Occasionally one sees acute heart failure not related to these factors which appears to be accompanied by a high cardiac output and may be related to the uremia itself Acute spontaneous potassium intoxication is a completely reversible complication which with adequate treatment is becoming less frequent Formerly it was a common cause of death High extracellular levels of potassium and more important a high extracellular intracellular ratio of potassium result from the catabolism of potassiu containing tissue and from the effect of uremia acidosis on the distribution of this ion n cell membrane This may r t upon the neuromuscular syst

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The most common and important sign both of tumors of the kidney and of the bladder is painless asymptomatic hematuria This may be microscopic gross or intermittent Its appearance particularly in the absence of proteinuria and cylindruria *requires rapid and thorough investigation of the entire* genitourinary tract Patients with tumors of the kidney may complain of vague pain or gastrointestinal symptoms as well as questionable fullness in the flank and upper abdomen Occasionally the passage of blood clots down the ureter may give colicky pain Specific symptoms however occur *relatively late in the disease and spontaneous pain*less bleeding is of the utmost importance The diagnosis is made by cystoscopy or by excretory urography or retrograde pyelography when indicated Cytologic examination of the urine for malignant cells may be an adjunct Arteriography may furnish valuable evidence in selected cases when the findings by pyelography are not definite The treatment for kidney tumors and tumors of the bladder is surgical

The kidneys are involved in the lesion of Hodgkin s disease in about 25 per cent of the cases but rarely is the involvement severe enough to yield renal failure unless pyelonephritis is superimposed

ACUTE RENAL FAILURE

The term acute renal failure implies sudden and *virtually complete failure of excretory function* This may be due to the rapid onset or progression of renal diseases already discussed e g acute glomerulonephritis malignant hypertension or fulminating pyelonephritis More frequently the phrase connotes an acute circulatory or toxic insult to previously normal kidneys resulting in sudden renal failure which is potentially largely reversible

Etiology The causes of acute renal failure are varied Specific toxins such as bichloride of mercury carbon tetrachloride diethyleneglycol and mushroom ingestion may be implicated Nonspecific *substances such as large amounts of sucrose* and the sulfonamides may be at fault In the latter instance either a specific sensitivity involving the kidneys in a vascular lesion or precipitation of insoluble sulfonamide compounds in the renal tubules may be causative During two world wars the syndrome has been recognized as attributable to cir*culatory disturbances such as profound* shock crushing injuries and other severe traumas It may follow severe hypotension occurring with myocardial infarction Incompatible blood transfusion and intravascular hemolysis from other causes (black water fever) may precipitate acute renal failure Among the infectious diseases responsible are *Weil s disease and hemorrhagic fever Bilateral* symmetric cortical necrosis of the kidney may be seen during the course of pregnancy—particularly but not necessarily when complicated by toxemias It may also occur in both sexes following severe hypotension Severe depletion of water and electrolytes presumably operating through circulatory *mechanisms may also result in acute renal failure* The conventional histologic sections of kidneys from patients who died with renal injury as a result of incompatible transfusions shock and crushing injuries indicated that the necrotic lesion was limited to the distal tubule The term *lower nephron nephrosis* was therefore coined for this pathologic entity *More recently workers studying* whole nephrons teased out and reconstructed from similar cases have found that the lesion is not limited to the distal tubule and it appears that acute tubular necrosis is to be preferred to the previous nomenclature Two types of lesions are described in these studies

1 A nephrotoxic necrosis caused by specific toxins in which the lesion is limited to the proximal tubules which are functionally concerned with the resorptive handling of the filtered toxins The lesion here is necrosis *of the epithelial cell with desqua*mation and disintegration of the tubular epithelium The cellular lumen may be filled with nuclear debris and cellular detritus All nephrons are equally involved since the distribution of the toxin is by way of the bood stream

2 The second characteristic lesion is disruption *of the integrity* of the renal tubule (tubulorhexis) with actual leakage of tubule contents into the interstitium These lesions are scattered among the nephron and may appear in any part thereof Ischemia is thought *to be responsible for* the production of this random damage since ischemia regularly produces irregular and spotty distribution of blood flow through the cortex Such damage may be seen at its maximum in the intermittent ing of the wedge shaped areas of infar

cortical necrosis In this latter syndrome the afferent arteriole and glomeruli may be involved as well In the experimental production of these lesions and in the pathologic picture there is evidence for the operation of a shunt of blood from the cortex through the medulla by way of the juxtamedullary glomeruli as suggested by earlier work Since however severe specific nephrotoxic insults are usually accompanied by circulatory disturbances the lesion here may be mixed and the common denominator may be ischemia Interstitial edema and loss of the tubular basement membrane were seen in both types of lesions The random regeneration of proliferating epithelial sheets as well as the persistent disruption of the tubular wall suggests that function in the nephrons may be permanently destroyed Although recurrent intravascular hemolysis with hemoglobinuria has been proved to cause a diffuse fibrotic process in the kidneys the relation of the heme pigment cast per se to the tubular damage is put in doubt by the lack of relation between tubular damage and the proximity of the pigment cast

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syndrome The therapeutic approach must first concern itself with the search for reversibility in the underlying disease process Failing this the therapist must realize that overtreatment may be more dangerous than intelligent neglect To attempt to maintain a normal chemical pattern in the face of advanced renal failure is to neglect the obvious possibility that a normal serum bicarbonate concentration for example may not be "normal for the patient with marked retention of acid metabolites that in the latter instance it is in effect a compensatory mechanism by which the more important factor of pH is stabilized The enthusiastic therapist is not infrequently surprised at the improvements which result when in discouragement he has abandoned attempts to force diuresis correct acidosis and maintain normal hemoglobin levels by transfusion

Treatment of Acute Renal Failure The first principle of the treatment of acute renal failure is to correct if possible the underlying defect This includes correction of hypotension the restoration of fluid and electrolyte losses and the appropriate therapy for obstruction A seriously dehydrated patient may have already sustained a tubular lesion in which case no amount of saline or blood will result in diuresis and indeed supplying these fluids may lead to overhydration which may produce circulatory embarrassment at a later date In spite of this possibility replacement therapy must always be given when clinically indicated but given cautiously As previously mentioned the deposition of heme pigment casts in the tubules is not the prime factor in the tubular lesions Therefore the use of intravenous alkali following intravascular hemolysis (e g with incompatible transfusion) in an attempt to increase hematin solubility must be reevaluated In any case if the renal tubules can alkalinize the urine in response to bicarbonate or lactate infusion no more than 5 Gm is necessary More than this does not increase the probability of prevention of heme damage and may greatly aggravate the problem if the renal lesion is such that the sodium cannot be excreted For a specific heavy metal intoxication such as mercury intoxication BAL should be administered although by the time the renal lesion has occurred the efficacy of BAL may be minimal Decapsulation of the kidney spinal anesthesia and intravenous procaine have no proved therapeutic value in the treatment of acute renal failure Lavage of the renal pelvis with warm bicarbonate solution may be attempted for sulfonamide concretions but otherwise has little value Cortisone and ACTH therapy to prevent inflammatory response and renal edema has been tried but without success

Once it is apparent that the renal lesion has occurred and severe oliguria supervenes the problem then becomes one of maintaining the patient in the optimal state until spontaneous healing and diuresis take place A first consideration is that of *caloric requirements* Since it is the products of protein catabolism which in large part give rise to the toxic metabolites that accumulate in renal failure to minimize protein catabolism becomes a prime aim of therapy The protein sparing effects of the administration of glucose and fructose are well known Emulsions of fat which have an even higher caloric value per unit weight have been advocated Since however acute renal failure tends to be a self limited disease usually occurring in well nourished individuals with adequate stores of body fat it would seem wise to permit them to burn endogenous fat rather than to force upon them the fatty emulsions which may well aggravate nausea vomiting and diarrhea with resultant electrolyte losses—effects that in themselves present more serious problems In the author s experience it has been a satisfactory method of treatment to administer glucose solutions alone This is best accomplished by the use of a 50 per cent solution of glucose and water administered in a slow constant drip by means of a plastic catheter placed in one of the larger veins by insertion and threading through the saphenous vein or an antecubital vein after introduction through a No 13 needle This location in a large vessel minimizes venous irritation and the thrombosis which may result. The catheter should be shifted from one side to the opposite side every 6 days to diminish the risk of infection and thrombosis Its placement through an arm vein is to be preferred because the possibility of thrombophlebitis and embolism is greater from the lower limb veins For patients suffering from nausea and vomiting all oral intake should be kept to minimum although occasionally small amounts of buttered toast and sweet tea may be tolerated

After correction of existing losses *fluid* should be limited to replacement amounts only The total volume should be calculated from amounts lost by way of the gastrointestinal tract, plus an insensible loss of 0 5 ml/kg body weight/hr with increments for fever and for obvious sweating Insensible losses may be greatly increased by activity and the basal losses per kg body weight are much greater in children than in adults Recent evidence that endogenous water production from fat catabolism may be greater than previously estimated may necessitate keeping the figure for fluid replacement even lower than calculated on this basis When only 300 ml of fluid per day is indicated the provision of the minimal glucose requirements (150 Gm per day for the adult) in this amount necessitates its administration by the method described Wherever possible daily weights should be checked since it is obvious that if inadequate calories are provided

pression and finally loss of deep tendon reflexes and progressing to complete paralysis The cause of death is the resulting disturbance in the conducting system of the heart which may give rise to ventricular arrhythmias and death Electrocardiographic changes are characteristic and pass through a typical sequence beginning early with high pointed T waves in the precordial leads and a spread of the QRS complex with depression of the P waves in the standard leads and a sloping S T segment These changes may progress until the complexes resemble a sine wave at which time ventricular fibrillation may result as the terminal episode

Diuretic Phase Diuresis may begin at any time up to 6 weeks Rarely the urine volume may increase rapidly progressing from 20 to 30 ml per day to 2 500 ml within a 24 hr period Such rapid increases suggest renal vascular spasm as an etiologic factor in the oliguria More characteristic however is a stepwise increase in volume with increments of 200 to 300 ml per day An occasional patient may reach a plateau at 500 to 600 ml per day which persists for a week or more It is possible in these instances that a few nephrons capable of producing such a volume recover more rapidly than the bulk of the nephron population It is important to keep in mind that less than a liter of poorly concentrated urine particularly in the presence of infection and resorption of blood or necrotic tissue is frequently totally inadequate for amelioration of uremia The large urinary losses of sodium chloride and water which may occur during the diuretic phase have been stressed In patients who have been overhydrated however or in whom the metabolic production of water has been excessive such a diuresis may represent only loss of excess extracellular fluid and the accompanying weight loss may be beneficial In others true negative balance may result necessitating replacement Potassium losses also may be excessive Early in the diuretic phase one may see a continued rise of nonprotein nitrogen and even potassium in spite of urinary volumes of over 3 l per day A series of patients has been described in whom marked retention of sodium hypernatremia and central nervous system signs occur during the diuresis following anuria A frequent complication of the diuretic phase may be renal infection as evidenced by pyuria with or without clinical signs of pyelonephritis Otherwise the blood chemical picture usually returns to normal gradually renal function tests improve although a mild anemia and an inability to concentrate the urine may persist for some months

Prognosis In the uncomplicated case the prognosis is good if the patient is well managed Causes of death during the oliguric phase are congestive heart failure acute pulmonary edema convulsions potassium intoxication and more usually sequelae of the concomitant trauma which precipitated the acute renal failure The more sensitive tests of renal function may indicate permanent impairment following an acute episode although there may be no nitrogen retention or other chemical evidence of renal failure Unlike the changes of pyelonephritis or glomerulonephritis these changes do not appear to be progressive

CHRONIC RENAL FAILURE

The clinical picture of chronic renal failure is largely that of the associated hypertension and uremia which has been discussed in Chaps 20 and 227 The progression varies somewhat with the etiology Thus renal failure due to polycystic disease and nephrocalcinosis may run a slower and more benign course than that of chronic glomerular nephritis possibly because of the slower tempo of nephron destruction In general however the degree and rapidity of destruction of renal tissue and the magnitude of the associated hypertension determine the course which may be modified (but not reversed) by judicious treatment

Treatment of Renal Failure

By the term renal failure we imply inability of the kidneys to excrete the daily metabolic waste load presented for elimination The result of this is the retention of organic and inorganic metabolites which when marked gives rise to the clinical syndrome of uremia Regardless of our inability to explain it precisely these chemical abnormalities are responsible for the clinical signs and symptoms In general it is true that this is a chemical problem with which we have to deal and in the advanced stages it is independent of the type of renal disease which originates it The exception to this statement is the fact that some types of renal disease are more frequently accompanied by infection hypertension and more rapid progression which will then influence the clinical picture The correlation of any specific type of renal disease with these latter factors however is never so precise that it constitutes a real point in diagnosis and prognosis From the point of view of therapy as well as of prognosis we may well divide renal failure into the acute and chronic problems These differ by reason of the remarkable ability of the human organism to adapt to even marked chemical abnormalities if time for compensation is allowed Into this pattern too is woven the nutritional status and the adrenal activity of the acute and chronic patient In acute renal failure the causative agent may frequently be a therapeutic problem e g shock and the crush

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By the term renal failure we imply inability of the kidneys to excrete the daily metabolic waste load presented for elimination The result of this is the retention of organic and inorganic metabolites which when marked gives rise to the clinical syndrome of uremia Regardless of our inability to explain it precisely these chemical abnormalities are responsible for the clinical signs and symptoms In general it is true that *this is a chemical problem* with which we have to deal and in the advanced stages it is independent of the type of renal disease which originates it The exception to this statement is the fact that some types of renal disease are more frequently accompanied by infection hypertension and more rapid progression which will then influence the clinical picture The correlation of any specific type of renal disease with these latter factors however is never so precise that it constitutes a real point in diagnosis and prognosis From the point of view of therapy as well as of prognosis we may well divide renal failure into the acute and chronic problems These differ by reason of the remarkable ability of the human organism to adapt to even marked chemical abnormalities if time for compensation is allowed Into this pattern too is woven the nutritional status and the adrenal activity of the acute and chronic patient In acute renal failure the causative agent may frequently be a therapeutic problem e g shock and the crush

syndrome The therapeutic *approach must first concern* itself with the search for reversibility in the underlying disease process Failing this the therapist must realize that overtreatment may be more dangerous than intelligent neglect To attempt to maintain a normal chemical pattern in the face of advanced renal failure is to neglect the obvious possibility that a normal serum bicarbonate concentration for example may not be "normal for the patient with marked retention of acid metabolites that in the latter instance it is in effect a com*pensatory mechanism by* which the *more important* factor of pH is stabilized The enthusiastic therapist is not infrequently surprised at the improvements which result when *in discouragement he has aban*doned attempts to force diuresis correct acidosis and maintain normal hemoglobin levels by transfusion

Treatment of Acute Renal Failure The first principle of the treatment of acute renal failure is to correct if possible the underlying defect This includes correction of hypotension the restoration of fluid and electrolyte losses and the appropriate therapy for obstruction A seriously dehydrated patient may have already sustained a tubular lesion in which case no amount of saline or blood will result in diuresis and indeed supplying these fluids may lead to overhydration which may produce cir*culatory embarrassment at a later date* In spite of this possibility replacement therapy must always be given when clinically indicated but given cau*tiously As previously mentioned the deposition of* heme pigment casts in the tubules is not the prime factor in the tubular lesions Therefore the use of *intravenous alkali following intravascular hemoly*sis (e g with incompatible transfusion) in an attempt to increase hematin solubility must be reevaluated In any case if the renal tubules can alkalinize the urine in response to bicarbonate or lactate infusion, no more than 5 Gm is necessary More than this does not increase the probability of prevention of heme damage and may greatly aggravate the problem if the renal lesion is such that the sodium cannot be excreted For a specific heavy metal intoxication such as mercury intoxication BAL should be administered although by the time the renal lesion has occurred the efficacy of BAL may be minimal Decapsulation of the kidney spinal anesthesia and intravenous procaine have no proved therapeutic value in the treatment of acute renal failure Lavage of the renal pelvis with warm bicarbonate solution may be attempted for sulfonamide concretions but otherwise has little value Cortisone and ACTH therapy to prevent inflammatory response and renal edema has been tried but without success

Once it is apparent that the renal lesion has occurred and severe oliguria supervenes the prob*lem then becomes one of maintaining* the patient in the optimal state until spontaneous healing and diuresis take place A first consideration is that of *caloric requirements* Since *it is the products of* protein catabolism which in large part give rise to the toxic metabolites that accumulate in renal failure to minimize protein catabolism becomes a prime aim of therapy The protein sparing effects of the administration of glucose and fructose are well known Emulsions of fat which have an even higher caloric value per unit weight have been advocated Since however acute renal failure tends to be a self limited disease usually occurring in well nourished individuals with adequate stores of *body fat it would seem wise to permit them to* burn endogenous fat rather than to force upon them the fatty emulsions which may well aggravate nausea *vomiting* and diarrhea with resultant electrolyte losses—effects that in themselves present more serious problems In the authors experience it has been a satisfactory method of treatment to administer glucose solutions alone This is best accomplished by the use of a 50 per cent solution of glucose and water administered in a slow constant drip by means of a plastic catheter placed in one of the larger veins by insertion and threading through the saphenous vein or an antecubital vein after introduction through a No 13 needle This location in a large vessel minimizes venous irritation and the thrombosis which may result The catheter should be shifted from one side to the opposite side *every 6 days to diminish the risk of infection and* thrombosis Its placement through an arm vein is to be preferred because the possibility of thrombo*phlebitis and embolism is greater from the lower* limb veins For patients suffering from nausea and vomiting all oral intake should be kept to minimum although occasionally small amounts of buttered toast and sweet tea may be tolerated

After correction of existing losses *fluid* should be limited to replacement amounts only The total volume should be calculated from amounts lost by way of the gastrointestinal tract plus an insensible loss of 0 5 ml/kg body weight/hr with increments for fever and for obvious sweating Insensible losses may be greatly increased by activity and the basal losses per kg body weight are much greater in children than in adults Recent evidence that endogenous water production from fat catabolism may be greater than previously estimated may necessitate keeping the figure for fluid replacement even lower than calculated on this basis When only 300 ml of fluid per day is indicated the provision of the minimal glucose requirements (150 Gm per day for the adult) in this amount necessitates *its admin*istration by the method described Wherever possible daily weights should be checked since it is obvious that if inadequate *calories are provided*

and the patient does not lose weight too much fluid has been given

Electrolyte requirements necessitate that the intake be potassium free since potassium intoxication is a potential hazard Chloride and sodium losses in the gastrointestinal tract should be replaced as indicated in view of the fact that more chloride is lost from gastric juice and more sodium from losses below the pylorus An increment of less than 1 Gm of sodium chloride for insensible loss may be added although this may be considerably larger in frank sweating In the author s view depression of serum sodium levels is not an indication for sodium therapy unless it can be proved that such levels are due to excess sodium loss Alternative explanations not requiring replacement therapy are intracellular movement of sodium metabolic readjustment of body fluid tonicity and dilution of concentrations by excess water production or administration The last is best treated by drastic water restriction as outlined above Infection should be vigorously treated since it results in increased protein catabolism The fact that there is no renal mechanism for the excretion of the chemotherapeutic agent chosen should be kept in mind In all cases adequate vitamin supplements should be given The administration of testosterone proprionate 50 mg a day may have value because of its anabolic effect *Congestive heart failure* must be treated in the usual manner (Chap 226) Improper fluid administration frequently precipitates this situation and it may be improved by restricting the fluid intake In many instances digitalis seems less effective than in congestive heart failure uncomplicated by uremia Because of the increased danger of arrythmias in uremic patients digitalis preparations should never be given intravenously The wisdom of treating mild to moderate degrees of *anemia* in the anuric patient by whole blood transfusion is in grave doubt In the author s view a hematocrit of 30 or less is the only indication for therapy which then should consist of small repeated transfusions of freshly drawn packed red blood cells

The hazard of *potassium intoxication* may be reduced by the use of cation exchange resin enemata Impaction of the material in the large bowel and the removal of sodium on the resin are problems to be considered Advanced degrees of potassium intoxication may be treated by hypertonic sodium bicarbonate sodium chloride and calcium gluconate and perhaps more effectively by the infusion of hypertonic glucose and insulin Where immediate treatment is necessary the sodium salts whose action is apparent in a matter of minutes should be used This consideration must be weighed against the potential hazard of giving a sodium load to an anuric patient The removal of potassium from the blood by use of the various forms of dialysis is more effective and of greater duration and may be employed when life is threatened For the symptomatic treatment of restlessness and convulsions rectal or intramuscular paraldehyde has been widely used magnesium sulfate intramuscularly (as discussed in Chap 227) may be more specific for the central nervous system manifestations Barbiturates if used should be of the variety metabolized by the liver (Seconal and Amytal) rather than those excreted by the renal pathway (phenobarbital barbital) Results with Promazine (Sparine) have apparently been extremely favorable During the *diuretic phase* the replacement of sodium and water losses should be influenced by the considerations mentioned previously Under these circumstances hyponatremia is a more valid indication for hypertonic sodium therapy The clinical response to such infusions may guide further therapy An occasional patient may retain sodium during the diuretic phase with a resultant marked hypernatremia and hyperchloremia This syndrome is frequently associated with central nervous system disturbances and a low urinary pH During the diuretic phase with volumes of urine greater than 1 500 ml per day dietary management need be less severe Under these circumstances the patient may be allowed by mouth anything which he desires and will tolerate It must be remembered however that urine volumes of less than 1 000 ml per day may possibly not be accompanied by clinical improvement Urinary tract infections during this period should be carefully watched for and treated In most of the cases of acute renal failure conservative measures of therapy as outlined above will suffice In situations complicated by severe trauma or infection where the protein catabolism is rapid and the clinical situation deteriorating the *artificial removal of metabolites* may be an important therapeutic adjunct and in some cases life saving Exchange transfusions peritoneal lavage and lavage of the large bowel have been reported with varying degrees of success Lavage of the small bowel by means of a double lumen in dwelling tube and the use of the artificial kidney which affects extracorporeal dialysis of blood appear to have been most successful in this regard Both procedures are effective only if utilized by experienced operators

Treatment of Chronic Renal Failure The patient with chronic renal failure too may have a remediable lesion In this regard interference with the bladder outflow or obstruction of the ureters due to metastatic carcinoma or endometriosis must be considered Potentially reversible renal involvement includes the metabolic disorders previously discussed having to do with calcium and phosphorus metabolism The state of chronic renal failure frequently manifests the many compensatory mechanisms which may adjust to slowly progressive

nitrogen retention An understanding of these mechanisms may help to prevent mistaking a compensatory adjustment for an "abnormality" (Chap 19) In the first stage of renal failure polyuria may result in large fluid losses Since at this stage the clinical situation has not markedly deteriorated the patient is subjectively able to regulate his own intake according to need Intake in this case prescribed by the physician should be aimed at replacement and an adequate urine volume rather than an attempt at forced diuresis There is evidence that the polyuria may be the result of an osmotic diuresis occasioned by the imposition of a relatively large solute load (per nephron) on remaining functional renal tissue This might account in part for sodium losses and would make of questionable value attempts to force a diuresis with large water intakes The inability of the kidney to substitute ammonia and hydrogen ion for sodium plus the large urine volume may result in sodium losses of considerable magnitude

In the so-called salt losing nephritis" which may represent a particular renal lesion rather than a phase of renal decompensation losses of from 12 to 15 Gm of sodium chloride per day have been described and added dietary salt must be given In the usual case of early polyuric uremia appetite is adequate to replace these losses by voluntary increases in intake Recurrent infection or a surgical procedure by interfering with voluntary intake *may result in negative balance In such patients* parenteral fluid and electrolyte therapy may bring about dramatic improvement Drastic restriction of sodium for the treatment of hypertension is obviously contraindicated in the presence of renal failure An occasional patient with renal failure loses large amounts of potassium and has symptoms of weakness fatigue and even flaccid paralysis which may be ameliorated by administration of potassium There is good evidence that among such patients some may have primary disease of the adrenal cortex manifested by hypersecretion of aldosterone In advanced severe chronic renal failure sodium therapy for hyponatremia may be evaluated in terms of etiology Chronically debilitated patients frequently show depressions of serum sodium level which are the result of disturbed equilibration between cells and extracellular fluid and are not amenable to replacement therapy On the other hand sodium depletion may produce hyponatremia which in itself may aggravate renal failure If this problem cannot be solved by clinical evaluation a cautious trial of sodium therapy is in order This is best given by mouth or failing this as 3 per cent solution intravenously Similarly the treatment of acidosis with sodium bicarbonate or lactate in the uremic patient necessitates a consideration of the development of the acidosis The retention of acid metabolite rather than loss of sodium may be at fault in which case alkali therapy would not be indicated Furthermore alkali therapy by depressing ionized calcium may produce tetany Unfortunately there are no rules of thumb by which the proper intake of sodium and water can be calculated In general the physician must seek to obtain some idea of the average output under optimal conditions of well being and attempt to regulate the intake accordingly Therapy aimed purely at correcting chemical evidence of dehydration or hyponatremia is often misdirected and must be guided by the principles mentioned above

Although in the experimental animal an increased protein intake may aggravate renal disease and hasten the progression of uremia precise evidence for this at the clinical level is lacking Thus a moderate intake of protein in chronic renal failure would seem advisable Some amount of exogenous protein is necessary to replace urinary and wear and tear losses and to supply enzyme and hormone building blocks Further the addition of some protein to an otherwise restricted diet makes the whole intake somewhat more palatable and thereby facilitates total caloric intake For the adult patient 0 5 to 0 7 Gm of protein per kg body weight seems a reasonable value in view of a possible marked difference between the dietary protein described and that actually ingested As in acute renal failure the protein sparing effect of nonprotein calories *is important In this instance however fat calories* become of much greater importance since with prolonged illness fat stores do become depleted Here the oral ingestion of an emulsified fat preparation may be of real value A supplement of emulsified fat and glucose (Lipomul) providing 400 calories per 100 ml and taken in 50- or 100-ml doses flavored with coffee extract or chocolate 5 i d may be a valuable caloric adjunct Aluminum hydroxide gels such as Basaljel in 30 ml doses 5 i d will decrease phosphate absorption and tend to ameliorate acidosis The treatment of chronic anemia should be guided by the precepts in the preceding paragraph The administration of cobaltous chloride no longer has a place in routine therapy Congestive heart failure should be treated as in other instances with the precautions mentioned for acute renal failure In this regard it is probable that the so-called uremic lung is largely if not entirely due to the pulmonary congestion of heart failure The use of paraldehyde and Sparine for sedation is of value Topical applications of dilute acetic acid solutions may be tried for pruritus Morphine should be used cautiously because of aggravation of itching and vomiting The treatment of nausea and vomiting by anything except restriction of all intake has rarely been successful although effective use has been made of chlorpromazine (Thorazine) in doses of

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Electrolyte requirements necessitate that the intake be potassium free since potassium intoxication is a potential hazard Chloride and sodium losses in the gastrointestinal tract should be replaced as indicated in view of the fact that more chloride is lost from gastric juice and more sodium from losses below the pylorus An increment of less than 1 Gm of sodium chloride for insensible loss may be added although this may be considerably larger in frank sweating In the author s view depression of serum sodium levels is not an indication for sodium therapy unless it can be proved that such levels are due to excess sodium loss Alternative explanations not requiring replacement therapy are intracellular movement of sodium metabolic readjustment of body fluid tonicity and dilution of concentrations by excess water production or administration The last is best treated by drastic water restriction as outlined above Infection should be vigorously treated since it results in increased protein catabolism The fact that there is no renal mechanism for the excretion of the chemotherapeutic agent chosen should be kept in mind In all cases adequate vitamin supplements should be given The administration of testosterone proprionate 50 mg a day may have value because of its anabolic effect *Congestive heart failure* must be treated in the usual manner (Chap 226) Improper fluid administration frequently precipitates this situation and it may be improved by restricting the fluid intake In many instances digitalis seems less effective than in congestive heart failure uncomplicated by uremia Because of the increased danger of arrythmias in uremic patients digitalis preparations should never be given intravenously The wisdom of treating mild to moderate degrees of *anemia* in the anuric patient by whole blood transfusion is in grave doubt In the author s view a hematocrit of 30 or less is the only indication for therapy which then should consist of small repeated transfusions of freshly drawn packed red blood cells

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appears to remove enough metabolite to be of real value in the treatment of uremia

Homotransplantation of the human kidney is therapeutically successful only when performed between identical twins The possibility of effecting a "cure for chronic renal disease by modifying the fundamental response of the rejection of a homograft is an exciting prospect for the future

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Section 4 The Respiratory System

The reader's understanding of the specific pulmonary disorders discussed in this section will be aided by prior perusal of Chaps 10 11 and 12 which deal with the common causes and mechanisms of such important manifestations as dyspnea cough hemoptysis and cyanosis Tuberculosis pneumonia and other specific infections of the lung are considered in the chapters on infectious diseases cor pulmonale and asthma respectively are discussed in Chaps 224 and 210 The treatment of chronic respiratory insufficiency will be found on p 1390 and acute respiratory failure is considered on pp 1392 and 1772

233 DISORDERS OF THE CHEST WALL AND MEDIASTINUM

John S Chapman

ANOMALIES AND DISORDERS INVOLVING CHEST WALL

The commonest anomalies of the chest wall are developmental abnormalities of the ribs which include bifidism agenesis of certain ribs cervical ribs and lumbar ribs Clinically these conditions are usually of little or no significance except as cervical ribs occasionally give rise to brachial plexus pain or obstruction of the subclavian vessels To the thoracic surgeon they may assume considerable importance in the planning of thoracoplasty The ribs are common sites for osseous metastases from visceral carcinoma and their involvement in multiple myeloma is usual The deeper muscles of the chest are invaded early by carcinoma of the breast and extension directly into bone may occur The skin of the chest wall may be involved in dermatomyositis and in scleroderma and extension of lupus erythematosus over the flush area of the upper chest may occur

Severe *scoliosis* or *kyphoscoliosis* is frequently associated with bronchiectasis on the compressed side while functionally the derangement of the thorax is a common source of dyspnea

Pigeon chest marked by a tremendous anteroposterior diameter of the thorax and a prominent prowlike sternum seems not to impair ventilatory or alveolorespiratory function and is clinically of importance chiefly in differentiation from the barrel chest of emphysema

Funnel chest is much more important from the standpoint of functional disorder On occasion the sternum may be so markedly depressed as to displace the heart into the left axilla while the rib motion is so much impaired that respiration becomes almost exclusively diaphragmatic This disorder which is apparently familial is readily recognized in early life and is amenable to various surgical procedures Results are most satisfactory if operation can be performed in childhood

Injuries of the thorax which are associated with multiple rib fractures or separation of the sternum from the ribs are of as much concern to the internist as to the surgeon The patient usually presents the picture of severe shock associated with marked embarrassment of respiration cyanosis and great pain One observes that the unsupported chest wall moves in a paradoxic manner the sternum or affected side being drawn inward during inspiration Numerous rhonchi are audible In addition traumatic pneumothorax with subcutaneous and

10 to 20 mg intramuscularly or 15 to 25 mg by mouth Moderate hypotension and drowsiness may be undesirable side effects The treatment of hiccough by carbon dioxide inhalation may be of temporary benefit In the absence of vascular disease the use of the artificial kidney in chronic renal failure may give striking but temporary remissions Homotransplantation of the human kidney has been attempted with recorded survival and adequate function for a period of 5 months in one instance This approach to therapy is interesting since it is aimed at curing chronic renal disease The complexity of the immune responses involved however makes it improbable that the procedure will be of more than temporary value in the near future In severe chronic renal failure particularly if accompanied by hypertension attempts at rigorous therapy may yield benefits not commensurate with the discomfort to the patient caused by enthusiastic efforts With this in mind the wise therapist may discontinue efforts at rigid dietary restriction parenteral supplements and painful procedures Not infrequently the wisdom of this choice may be manifest in a period of improved well being before the disease is mercifully concluded by a myocardial infarction or acute potassium intoxication

Extrarenal Removal of Metabolites in Uremia A number of techniques have been devised for the artificial removal of metabolites or toxic substances in cases of renal failure Of these the so called artificial kidneys are perhaps the most effective The artificial kidney is in reality a dialyzer and a number of different models have been constructed These vary in size and shape and in the manner of their construction but the fundamental principle of their operation depends upon the diffusion of substances from blood through a semipermeable cellophane membrane into a bath fluid so constituted that there is no diffusion gradient from blood to bath for substances whose removal is not desired Such a gradient from blood to bath is created for molecules whose removal is desired by omitting them from the bath fluid A major advantage of this technique is that each diffusible substance moves across the cellophane membrane primarily as a result of the concentration difference which exists on either side of the membrane and this transfer is independent of the concentration of other diffusible substances

Present indications are that such an apparatus may be used as an adjunct to good conservative measures of treatment in acute renal failure It should not be considered an alternative since the use of dialysis may greatly facilitate medical management by correcting the chemical imbalance decreasing nausea and vomiting and improving drowsiness and semicoma In acute renal failure complicated by fever infection or trauma where protein catabolism and consequent accumulation of metabolites are rapid conservative measures may be ineffective and actual removal by dialysis can be essential to treatment In this sense the use of dialysis to remove potassium in acute *spontaneous* potassium intoxication has a special significance

Other clinical situations in which dialysis has proved useful are the treatment of exacerbations of chronic renal disease and the preparation of the patient with chronic renal failure for surgical procedures In slowly progressing chronic renal failure hemodialysis in properly selected cases may give months of useful comfortable life after conservative measures have failed The type of case suitable for such treatment is the chronic uremic patient without significant hypertensive cardiovascular disease and with an adequate urine volume The removal of exogenous toxins in situations where renal function has failed may also be a useful function of the artificial kidney Such instances are aspirin poisoning and barbiturate intoxication in the presence of a renal function inadequate because of shock In bromide intoxication the artificial kidney has a particularly useful role since the predominantly extracellular position of the bromide ion makes it easily removed by dialysis and because resorption of filtered bromide by the normal renal tubule makes the usual methods of treatment slow The use of the various forms of artificial kidneys should not be reserved for terminal moribund patients since experience indicates that it has a real role in therapy which is best performed in conjunction with other forms of treatment Artificial kidneys operated by trained and experienced teams with adequate facilities in large centers may serve as a source to which may be referred patients for whom conservative methods of therapy alone are not adequate Although simpler cheaper artificial kidneys may be built there is no inexpensive way to construct a physician well versed in the complex problems of its use

The use of peritoneal irrigation by older techniques employing operative procedures on the abdomen have now largely been abandoned since use of this procedure must necessarily be prolonged in order to achieve effective nitrogen removal and this almost inevitably led to infection Simpler methods over shorter periods however have been devised employing plastic tubes in conjunction with ordinary parencentesis techniques Such methods are effective in correction of electrolyte abnormalities although of much less value in the removal of other metabolites The relative simplicity of the technique however makes it a useful one in small hospitals Lavage of various portions of the intestinal tract employing a number of different techniques has been reported When used with care and by trained teams lavage of the small intestine

usual etiology of dyspnea is concerned On fluoroscopy the diaphragm is seen to present a very rapid jerky incoordinate motion The condition may develop quite suddenly and cease equally rapidly The cause of the phenomenon is not known but it is thought to arise from some type of phrenic nerve or muscular irritation not unlike the mechanism involved in hiccough

DISEASES OF MEDIASTINUM

The only tissue that can be considered truly mediastinal is the loose areolar tissue and fat which lie among traversing structures In health the mediastinal structure is so elastic that displacement readily occurs from slight changes in pleural pressure and even from a change from one lateral decubitus to the other *Mediastinal shift is common* in diseases of the lung or pleura and takes place when pneumothorax is present for long periods Variation of position of the mediastinum with phases of respiration indicates either unilateral air trapping blocked bronchus or fibrosis of the lung

Mediastinitis

Primary syphilitic mediastinitis and tuberculous mediastinitis have been described and other primary infection may occur A type of mediastinitis associated with viral invasion of the tracheobronchial tree is recognized infrequently but in fact, may be quite common The organism probably reaches the tracheobronchial nodes where it sets up a lymphadenitis that results in fever a sense of retrosternal oppression and poorly localized pain in the center and upper portion of the chest Since the enlargement of the lymph nodes is so slight the condition is not evident in roentgenograms and one can only suspect its existence It is fairly well substantiated by autopsy that mediastinal lymphadenitis whatever the infecting agent may well be the precipitating factor in the development of pericarditis

The more dramatic type of mediastinitis a spreading pyogenic inflammation or acute abscess is the result either of severe derangement of the organs which lie within the mediastinum or of descending infection from acute retropharyngeal or cervical abscess The disease is marked by high fever marked retrosternal pain which may be referred to the back, difficulty in breathing a cough of a pressure type and dysphagia At times films at various angles fail to demonstrate clearly the inflammatory process in which case diagnosis is most difficult in other cases roentgenograms may reveal considerable widening of a portion of the mediastinum and even the fluid level of abscess In every patient with cervical or retropharyngeal abscess the physician should keep in mind the possibility of mediastinitis and should be on the alert for symptoms

Although diseases (notably cancer) of the bronchus may rarely perforate and lead to mediastinitis the most common cause by far is disease of the esophagus Perforation may result from missiles from rough instrumentation from attempted dilatation of strictures and even when the greatest care is used from passage of the esophagoscope into pouches or diverticula Spontaneous perforation may follow neurosurgical procedures and spontaneous rupture may occur during retching and vomiting Ulceration is seen in association with peptic esophagitis with severe burns involving a large area of the body surface (*Curling's ulcer*) and above all, with carcinoma of the esophagus

In all these situations the patient presents the *picture of severe acute illness superimposed on* cachexia, if carcinoma is the cause or associated with shock in the event of acute perforation Gases at once enter the mediastinum along with infected secretion and may produce Hamman's sign. If the volume of gas is large it may dissect its way into the neck where subcutaneous emphysema will be demonstrable Pain is frequently intense and may radiate to the back or upward into the neck

X ray recognition depends upon the demonstration of streaky or patchy translucent areas overlying the mediastinal structures In patients who survive long enough widening of the mediastinum and fluid level may be present

Surgical exploration and drainage is urgently indicated, with repair of the defect if its nature permits Penicillin in doses of 10 million units daily is necessary

Pneumomediastinum

This condition may be either traumatic or spontaneous The escape of gases into the mediastinum is also frequent in perforation of the herniated stomach or of the esophagus Traumatic pneumomediastinum is usually associated with chest wall injury of considerable magnitude In patients who have suffered trauma, the escape of gas is rapid and dissection through the mediastinum into the neck occurs within a short time Hamman's sign, a to-and fro crunching, clicking or tapping (as variously described) is audible over the precordium The cardiac dullness is reduced in area and the heart sounds commonly are distant Crepitation of the subcutaneous tissue is readily palpable in the neck and sometimes over considerable areas of the body The x ray reveals extensive widening of the mediastinum, with large streaks of gas separating the major structures

Neither the pneumomediastinum nor the subcutaneous emphysema constitutes a very serious threat to the patient, though disfigurement may be severe

mediastinal emphysema frequently is seen as a result of laceration of the lung Hemoptysis and bleeding into the pleural cavity are by no means rare

The patient s condition requires immediate and well considered measures Shock and hemorrhage call for transfusion of whole blood Tension pneumothorax if present demands immediate decompression even with the use of continuous suction if the escape of air is rapid The presence of blood and secretions in the airways necessitates bronchial aspiration at frequent intervals Although one or two injections of morphine may be necessary during the acute emergency this drug should be discontinued as soon as possible since its depressant action on the cough reflex and the respiratory center tends to perpetuate and aggravate both bronchial obstruction and hypoxia Intercostal nerve block successfully performed is far more efficient in relieving pain and has none of the disadvantages of the use of narcotics As the patient emerges somewhat from severest danger the problem of the immobilization of the flailing chest wall arises Heavy adhesive strapping markedly limits the motion of the chest wall but is a potent cause of retained secretions Sandbags offer quite as good immobilization without such great danger of atelectasis and pneumonia In extreme cases surgical fixation may be necessary to control paradoxic motion

Fractures involving the first rib on either side may have two grave complications Laceration of trachea and esophagus may occur with formation of tracheoesophageal fistula The subclavian vessels may undergo trauma from broken rib ends and traumatic aneurysm or arteriovenous fistula result

Another complication of severe trauma to the chest wall is laceration or even division of a major bronchus The condition must be suspected if following removal of gas and blood breath sounds remain absent and the side continues to exhibit radiologic opacity The recognition is important since bronchoplastic procedures result in recapture of completely normal function Planigraphic study of the major bronchial area reveals absence of the usual bronchial lucency while iodized oil demonstrates that the main bronchus ends blindly It is noteworthy that such bronchial injury may result occasionally from apparently trivial trauma

Infections of the chest wall are rarely of much moment but on occasion severe phlegmons may develop along the tract of an aspirating needle Tuberculous and actinomycotic pleurocutaneous fistulas may result either from repeated aspiration or rarely spontaneously Ribs cartilages or sternum are fairly frequent sites of tuberculous osteitis

Tumors of the chest wall commonly arise either from intercostal nerves or from ribs Fibromas sometimes persisting in benign form only to undergo sarcomatous degeneration later have been described

If the diaphragm may be considered a part of the chest wall its commonest disorder is *hiatus hernia* (see Chaps 4 244) Traumatic hernias occur chiefly on the left side and give rise to a confusing picture characterized by the manifestations of an acute surgical abdominal disorder as well as by those of acute respiratory embarrassment The involved side of the chest is motionless and breath sounds are absent but one may hear peristaltic sounds sometimes as high as the clavicle The roentgenogram of the chest commonly reveals marked shift of the heart and mediastinum into the normal side of the chest on the other dense side small radiolucent areas sometimes with fluid levels indicate the presence of bowel above the diaphragm A glass of barium suspension followed fluoroscopically will serve to remove any doubt

Eventration of the diaphragm a congenital anomaly usually involving the posterior leaf of the left half of the diaphragm may be mistaken on physical examination for pleural effusion or diaphragmatic elevation following phrenic paralysis Roentgenographically before the lateral view clearly reveals the nature of the lesion the suspicion is of hernia or phrenic paralysis

Paralysis of the diaphragm is of very great importance both from a functional and from a diagnostic point of view The diaphragm accounts for about two thirds of the ventilatory function and its paralysis may result in considerable embarrassment of respiration Paralysis has to be differentiated from eventration and from fixation by adhesions The discovery of paradoxic motion of the muscle when during fluoroscopy the patient sniffs indicates interruption of the phrenic nerve which has been a collapse measure frequently employed in tuberculosis Paralysis however may be the result of direct invasion of the nerve by carcinoma of the bronchus Rarely it may occur spontaneously as a result of twisting motion of the head and neck with the thorax in a strained position In the presence of what appears to be a spontaneous paralysis without evidence of tumor it is very important to be sure that the elevation of the diaphragm is not apparent Pleural fluids now and then accumulate beneath the lung and fail to take the ordinary meniscus curve on physical examination or x ray study Patients of this type frequently fail to show any motion of the supposed diaphragmatic shadow but before making a definite diagnosis of spontaneous paralysis one should attempt thoracentesis to make certain that the shadow is not produced by subpulmonary fluid

Diaphragmatic flutter is a rare phenomenon in which a patient complains of marked shortness of breath without apparent cause in so far as the

This space contains the aortic arch and its major branches (innominate, left subclavian and left common carotid origins), the innominate veins and the upper half of the superior vena cava, the trachea, esophagus, thoracic duct, thymus gland, some lymph nodes and the vagus, phrenic, left recurrent and cardiac sympathetic nerves.

To be found in the superior compartment are bronchogenic cysts, tuberculomas, thyroid and parathyroid adenomas, teratomas and metastatic tumors.

The *anterior* mediastinum is demarcated in front by the sternum, posteriorly by the pericardium and below by the diaphragm. It is a very meager space and contains normally only some areolar tissue, lymphatics, lymph nodes and branches of the internal mammary arteries.

In this space may be located teratomas, thymomas, lymphangiomas and any of those listed for the superior mediastinal space.

The *middle* mediastinum comprises the heart and its pericardial covering, the ascending aorta, the lower portion of the superior vena cava and its junction with the azygos vein, the bifurcation of the trachea, the proximal pulmonary arteries and veins, the phrenic nerves and some lymph nodes.

In this compartment may be found bronchogenic cysts and pericardial cysts or diverticula.

The *posterior* mediastinum is bounded in front by the heart, in back by the lower eight thoracic vertebrae and the shelving posterior portion of the diaphragm. It contains the thoracic descending aorta, the azygos and hemiazygos veins, the esophagus, the thoracic duct, the vagus and splanchnic nerves and some lymph glands.

In the posterior mediastinal compartment are typically found neurogenic tumors and also certain bronchogenic, esophageal and gastroenteric cysts.

Symptomatology. A majority of benign mediastinal tumors are asymptomatic and are discovered in the course of routine roentgenograms or those done for other purposes. With very few exceptions symptoms are not specific and are caused by complications which include pressure necrosis, secondary infection, hemorrhage and rupture of cystic lesions into a neighboring viscus. Thus fever, cough, dyspnea, wheezing, chest pain and hemoptysis may occur in any combination and sequence. Dysphagia is not a very common symptom.

Malignant tumors which invade extensively in the mediastinum tend to produce the so-called *syndrome of the superior vena cava*. This is manifested by edema of the neck, face and conjunctiva together with distention and increased pressure in the veins of the neck, chest and upper extremities. Epistaxis may occur, and also hoarseness from laryngeal edema or paralysis of the recurrent nerve. The patient may have severe headache,

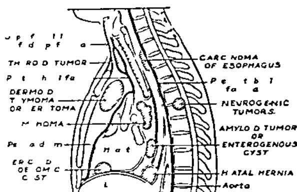


FIG 166 A much simplified lateral projection of the chest showing sites of predilection of various mediastinal tumefactions. (*Courtesy Dr John Chapman.*)

fainting spells and vertigo. This syndrome sometimes occurs with very large benign tumors such as thyroid adenoma, located in the superior aperture of the thorax.

One pathognomonic symptom of a particular mediastinal tumor is *trichoptysis* or the spitting up of hair, usually accompanied by sebaceous material. This occurs in the case of dermoid cysts, but only when fistulization into the tracheobronchial tree has taken place.

Differential Diagnosis. Certain lesions originating in structures outside the mediastinum proper can intrude themselves secondarily and give rise to confusion in diagnosis. Such include (1) substernal goiter, (2) diaphragmatic hernias, (3) tumors arising in the thoracic skeleton and (4) thoracic meningocele. In addition, aneurysms of the heart, aorta and great vessels and pericardial effusion may simulate tumor.

Substernal goiter usually arises as a nodular downward extension from a lower thyroid pole. There may be a palpable mass in the neck, the trachea tends to be compressed and deviated away from the side of the lesion. Radiographic continuity of the mediastinal mass with a cervical thyroid shadow is commonly seen. Radioactive iodine tracer techniques may be useful in doubtful cases.

The *diaphragmatic hernias* most likely to be confused with mediastinal tumor are those located in the parasternal foramen of Morgagni. These may be essentially solid lesions consisting of herniated omental fat. In the lateral radiographic projection they are based strictly in the anterior cardiophrenic angle. The air pattern of the transverse colon may be abnormally elevated; this can be further demonstrated by barium enema.

Chondroma, chondrosarcoma and *Ewing's sarcoma* arising in rib or vertebra may grow internally and expansively in certain cases. Careful roentgenologic study of the involved bone should lead to the detection of some changes, but these may be quite

at the time Only rarely is it necessary to make incisions about the base of the neck to permit the escape of gases Rather the attention should be directed to the chest wall and the pulmonary injury Infection seems to be quite rare

Spontaneous pneumomediastinum is said to occur predominantly in young males who previously have been in excellent health The pathogenesis as described by Macklin is the escape of air from the alveoli into the perivascular tissue of the lung from which the gas makes its way into the mediastinum The onset is sudden usually with severe pain retrosternally and often with radiation into the neck shoulders or arms so that coronary occlusion stands high in the differential diagnosis

The direct diagnosis depends upon the discovery of the crunch which is said to be audible in some patients only when they are placed in certain positions In a fairly high proportion of patients left sided pneumothorax may be demonstrable also

The radiographic signs of small pneumomediastinum are said to be unusual prominence of the aortic knob a very clear outline of the pulmonary arterial segment or a band of radiolucency lying along the border of the heart Most competent radiologists insist upon more definite signs than these—i e the demonstration of streaks or patches of gas in the mediastinum The usual projection is inadequate and oblique and lateral films at full expiration often prove more informative Since small left pneumothoraxes alone may produce a crunch indistinguishable from Hamman s sign conclusive proof of pneumomediastinum depends upon the elicitation of the crunch in the absence of a pneumothorax or upon the absolute demonstration of mediastinal gas by roentgenogram No treatment other than rest reassurance and mild analgesics is required The patient should be warned that the accident might recur

Tumors of the mediastinum are discussed in Chap 234

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234 TUMORS OF THE MEDIASTINUM

Gustaf E Lindskog

Mediastinal tumefactions may be classified according to their pathogenesis as follows true neoplasms (e g thymoma) congenital malformations (e g bronchogenic cysts) infections (e g tuberculomas) and degenerative lesions (e g arteriosclerotic aneurysms) True neoplasms may be primary or secondary and benign or malignant

Within the narrow confines of the mediastinum even the most benign and slowly growing tumor can on occasion produce irreparable damage to the host by mechanical encroachment compression and obstruction of vascular channels the esophagus and the tracheobronchial tree Infection may develop in cystic lesions from blood borne sources or by direct extension after erosion into the bronchi or into the esophagus A comprehension of mediastinal anatomy is therefore essential to the study of mediastinal tumors furthermore any attempt to define the pathologic nature of these lesions before surgical excision must lean heavily on their location in the mediastinal compartments since the different varieties of tumor have definite sites of predilection (Fig 166)

Anatomy of the Mediastinum The mediastinum as the name implies is a space lying between the right and left pleurae in or near the median sagittal plane of the thorax More for clinical purposes than for anatomic reasons the mediastinum has been divided into four compartments superior anterior middle and posterior

The *superior* mediastinum is bounded in front by the manubrium and behind by the upper four thoracic vertebrae Inferiorly it is demarcated by an imaginary line extending from the manubriogladiolar juncture to the fourth vertebral body

a sympathoma of neurofibromatous type (4) sympathicoblastoma, derived from primitive cells which are small, round, densely nucleated and with a tendency to pseudorosette patterns (5) paraganglioma including the rare hypersecreting variant pheochromocytoma

About 95 per cent of posterior mediastinal tumors are neurogenic in derivation, but neurilemmoma and neurofibroma may occur in a more lateral or peripheral situation in relation to the intercostal nerves An expansile growth located in an intervertebral foramen may enlarge the latter as demonstrated in roentgenograms by intrusion into the epidural space it can produce symptoms of spinal cord compression the so-called "dumbbell tumor

Ganglioneuromas exist principally in relation to the sympathetic chain and can produce the typical Horner s syndrome and sweating changes of the ipsilateral upper extremity Neurofibroma may be a local manifestation of von Recklinghausen s disease

Tumors of the Thymus. Tumors arising in the thymus gland are frequently difficult to identify and classify The two main cell types thymocyte (lymphocyte?) and reticulum (epithelial?) may be present in varying proportions Thymomas tend to be heavily encapsulated and lobulated fleshy or solid Microcyst formation is common but gross cystic changes can occur Microscopically perithelial arrangement of tumor cells around vascular lymphatic, or tissue spaces is rather characteristic Hassal s corpuscles are found in only about 25 per cent.

Malignant change in a thymic tumor is signaled by capsular infiltration and invasion of contiguous structures such as pericardium trachea, large vessels and pleura. Remote metastases are uncommon even in fatal cases

Thymic tumors are found in 15 to 20 per cent of myasthenia gravis cases and a significant number of patients with thymic tumors on careful analysis are noted to have myasthenic symptoms Thymectomy and excision of thymic tumors have an unpredictable effect upon the course of myasthenia gravis ranging from cure to no effect

Other Generally Benign Tumors of the Mediastinum Lipomas and fibromas are relatively rare They occur anywhere in the mediastinum and furnish the largest specimens some have been reported as heavy as 17 pounds Pressure symptoms are disproportionately mild

Lymphangiomas are typically cystic and located in the anterior mediastinum and cardiophrenic angle They are multilocular and demonstrate elastic tissue and smooth muscle in association with the mesothelium lined channels Cervical and mediastinal locations may be combined in the same case Spontaneous chylothorax has been reported and secondary infection but ordinarily these are asymptomatic tumors

Parathyroid adenomas usually occur in the expected distribution of the normal parathyroid glands In perhaps 20 per cent of cases they are located ectopically in the mediastinum Such adenomas are ordinarily quite small and are not often visualized by radiographic methods An outline of the esophagus with barium may be helpful The surgical treatment of hyperparathyroidism requires a complete search of the cervical area before the mediastinum is explored ideally in a single operation

Pericardial (Pericardiodiaphragmatic) Cysts and Diverticula Aberrations in the development of the pericardial sac may lead to the formation of pericardial diverticula or cysts These are unilocular thin walled sacs containing clear colorless fluid A simple endothelium lines the thin connective tissue wall Diverticula are rarer than cysts they communicate by a narrow ostium with the main pericardial sac whereas the cysts are separate and may even be at some distance from the pericardium They produce no symptoms as a rule and are removed only for diagnostic purposes

Primary Malignant Tumors The lymphoblastic series of tumors (lymphoma Hodgkin s disease and lymphosarcoma) constitute about 70 per cent of this category Various types of connective tissue malignancies also occur such as fibrosarcoma. Epithelial neoplasms independent of any demonstrable extramediastinal focus (such as the peripheral lung) are least common Some of these rarities may arise from the thymus from pharyngeal pouch remnants, or from degenerating teratoid lesions.

Hodgkin s disease (see Chap 220) may begin in the mediastinal nodes and remain apparently localized there More commonly there is relatively early involvement of the cervical, axillary or other peripheral lymph nodes this enlargement may constitute the first clinical evidence of the disease Splenomegaly occurs in about 70 per cent of Hodgkin s cases at some time in the course There may be itching of the skin. Systemic manifestations such as periodic fever malaise anorexia, and weight loss are more common with Hodgkin s disease than with lymposarcoma and reticulum cell sarcoma. The latter is sometimes confined to the region of the thymus when first recognized, only to spread later and produce the clinical picture of superior vena caval obstruction Pleural effusion may develop

Secondary Malignant Tumors The commonest tumor of the mediastinum is undoubtedly metastatic carcinoma. The site of origin may be an intrathoracic organ such as esophagus trachea, or

inconspicuous Pain is likely to be severe with malignant bone tumors and can simulate that caused by neurogenic tumors when it is segmental in type

Thoracic meningocele is a very rare lesion seen chiefly in middle aged females and associated with von Recklinghausen s disease (*café au lait* spots and multiple neurofibromatosis) Radiographic examination of the spine shows enlargement of several inter vertebral foramina

Aneurysms of the aorta and its major branches are of great concern in the differential diagnosis of mediastinal tumors They are discussed in Chap 229

Large *pericardial effusions pericardial cysts* and *idiopathic cardiac* hypertrophy may be confused radiologically and clinically with mediastinal neoplasms

Diagnostic Methods Physical examination should include a careful study for enlarged peripheral lymph nodes especially in the supraclavicular and axillary groups and for splenomegaly and hepatomegaly in connection with the malignant lymphomas Recurrent nerve paralysis should be ruled out by indirect laryngoscopy *Horner s syndrome* is usually a stigma of malignant infiltration of the upper dorsal sympathetic chain but may occur as a pressure effect from discrete and benign tumors This syndrome is characterized by narrowing of the palpebral fissure recession of the eyeball a contracted pupil and absence of sweating on the ipsilateral side of the face

Bronchoscopy is rarely of definitive value in the diagnosis of primary mediastinal tumors but may be required to rule out lesions such as bronchogenic carcinoma Bronchography employing iodized oil is neither helpful nor necessary unless obstructive complications in the lung require evaluation Sometimes the latter are at least as demanding of therapy as the causative tumor

A complete radiologic study includes fluoroscopy lateral and oblique roentgenograms as well as the standard PA projection A barium study of the esophagus should be carried out in every case of aneurysm and in the case of all tumors of the middle and posterior compartments Laminagrams may be very helpful The radiologist tries to determine among other things the presence or absence of encapsulation the existence of calcifications air and fluid levels intrinsic or extrinsic pulsations and the movement of the lesion during respiration and deglutition Of greatest importance is the position of the lesion in the mediastinal compartments characteristic locations are described under *Anatomy*

Surgical excision of a cervical axillary or other enlarged lymph node may be of great diagnostic value particularly when such diseases as Hodgkin s *tuberculosis and Boeck s sarcoid* enter the differential diagnostic picture

Even when lymph node enlargement is not detectable it is sometimes possible to establish a tissue diagnosis after *en bloc* resection of the small lymph nodes in the fatty tissue overlying the scalenus anticus muscle near its insertion

The commoner types of mediastinal tumors will be discussed briefly in terms of their special characteristics

Teratoid Tumors Benign teratoid tumors are commonly called dermoids They are usually large when first recognized ordinarily in the third and fourth decades More often unilocular than multilocular they contain sebaceous material and hair Dental structures and bone are sometimes present and cause characteristic radiographic densities The more complex teratomas are fleshy and contain *tissue recognizable as nervous system intestinal* tract pancreas kidney or testis and the like The capsules may be ill defined and infiltrated by carcinomatous or sarcomatous cells A predominantly unilateral development may lead to confusion with such tumors as seminoma and chorionepithelioma The complex teratomas have a very high incidence of malignant change with local invasion and metastases

Bronchogenic, Esophageal and Gastroenteric Cysts These are developmental anomalies of the primitive foregut and bronchial buds Commonly unilocular they are chiefly located in relation to the trachea upper bronchi and esophagus rarely they are found in the periphery of the lung or upon the diaphragm Communication with the air passages may preexist or develop later because of pressure The result is *pyocyst* and this may be associated radiographically with an air fluid level simulating pulmonary abscess

The majority of these cysts have a respiratory type of epithelial lining with ciliated columnar cells and pseudostratified basilar nuclei smooth *muscle cartilage and mucous glands may be present* Squamous and gastrointestinal types of lining cells are occasionally encountered principally in the cysts located about the distal esophagus The gastrointestinal types are prone to give rise to serious symptoms in the first year of life the others in adult life

Neurogenic Tumors Neurogenic tumors are the most frequently encountered of primary mediastinal neoplasms Several pathologic types are recognized (1) neurilemmomas derived from the sheath cells of Schwann (2) neurofibroma a more complex but usually benign lesion showing in addition to Schwann cells neuraxones and proliferated connective tissue (3) ganglioneuroma with ganglion cells in variable stages of maturity interspersed in

tuberculosis and actinomycosis Extension of infection through the diaphragm either by way of lymphatics or through direct erosion may produce pleurisy Commonly involving the right pleura particularly are amebic and bacterial abscesses of the liver a subphrenic collection of pus resulting from a perforated viscus and perinephric abscesses may be associated with pleural inflammation

Infarcts of the lung since they involve terminal vessels have at least one base on the pleura and sometimes two The pathologic changes produced therefore rather regularly involve the visceral pleural surface and result in the formation of fluid

Neoplasms of the lung either by metastasis or direct extension commonly reach the pleural surface and excite reaction whereas metastases from distant organs may seed the pleura directly or as in the case of carcinoma of the breast extend through the chest wall to produce disease of the parietal pleura

Finally collagen disease is frequently associated with pleurisy along with involvement of other serous cavities Typical of this group is disseminated lupus erythematosus but pleural disease may also be a feature of scleroderma and rarely, it may be associated with active rheumatoid arthritis In severe phases of active rheumatic heart disease the pleura may undergo similar reaction to that seen in the pericardium

The first pathologic change in acute pleuritis is redness edema and opacification of the surface followed soon by deposition of fibrin flakes over the center of the inflammation Such changes are manifest clinically as acute dry pleurisy The physical finding which corresponds with this phase of pleurisy is the coarse to and fro friction rub roentgen findings are not evident until fluid begins to accumulate in the pleural sac

As the disease progresses the acutely inflamed pleura begins to throw out an exudate which is at first usually serofibrinous Arrest of the process may take place either at the dry stage or at this stage but in the case of suppurative infections the fluid rapidly takes on the aspect of pus as greater numbers of neutrophils and large quantities of fibrin make their appearance In either the serofibrinous or purulent phase there is usually generalized chest pain frequently most severe in the lower thorax Dyspnea not only expresses voluntary and involuntary splinting of the chest but may be a result of considerable quantities of fluid Characteristic physical signs include a shift of the heart and mediastinum to the opposite side flatness and usually greatly diminished or absent breath and voice sounds The discovery of pleural fluid demands thoracentesis

The final or healed phase of any of these pleural reactions whether wet or dry serofibrinous purulent or bloody is the organization of pleural exudate The degree and extent of the resultant fibrous or adhesive pleurisy depend upon the amount of fibrin in the thorax and its distribution A small area of acute dry pleurisy may have as its residue only a thin filmy adhesion or as in the case of a tuberculous nodule a short thick cord Pleurisy that has produced great quantities of fibrinopurulent exudate or that has been associated with a considerable amount of bloody fluid may on the other hand give rise to marked pleural thickening with contraction of the entire hemothorax marked retraction of the heart and mediastinum into the affected side and elevation and fixation of the diaphragm Other physical findings consist of flatness to percussion very distant breath sounds and reduced tactile and vocal fremitus The condition is to be distinguished from acute pleurisy with effusion by the retraction and fixation of the affected side On roentgenographic study the displacement of the heart and mediastinum elevation of the diaphragm narrowing of interspaces and partial opacity of the lung field are characteristic In such instances particularly if the cause of the fibrothorax has been either tuberculous empyema or hemothorax extensive calcification of the pleura may be a late result A lung so encased may be almost without function

Inflammatory Pleural Fluids For purposes of this discussion all fluid that reveals the presence of inflammatory cells even though they are relatively few and even though the stimulus may be so comparatively innocuous as a small amount of blood in the pleura will be regarded as exudates Pathologically such differentiation is correct it avoids the uncertain terms *exudate* and *transudate* which could be clinically realized only by ignoring the numerous instances in which fluids manifested some characteristics of each type

It is more useful to describe characteristic inflammatory fluids than to attempt to set arbitrary and unreliable standards of differentiation One extreme of inflammatory pleural fluid is that associated with pneumonias The material obtained consists of pus has a high specific gravity may coagulate and contains innumerable cells An intermediate serofibrinous fluid such as may be encountered in tuberculous pleurisy or in a partially treated pneumonia is likely to have a specific gravity of around 1 018 a protein content of 1 5 Gm or more and cells numbering from 200 to 2 000 varying from a slight preponderance of polymorphonuclear cells to a vast preponderance of lymphocytes The other extreme consists of a thin fluid with a specific gravity sometimes as low as 1 012 with very little protein but with perhaps as many as 200 to 300

bronchi Mammary cancer is a frequent invader however and remote neoplasms such as renal and ovarian carcinoma may metastasize to lymph nodes and subsequently extend more diffusely in the mediastinal tissues

Extension to mediastinal lymph nodes is an important limiting factor in the surgical treatment of mammary carcinoma Its frequency has led to the recommendation that preliminary biopsy of the internal mammary chain of nodes be performed in cases where the primary breast lesion is situated in the medial quadrants and when the axillary lymph nodes are palpably involved

Isolated lymph node metastases in the mediastinum may be quite asymptomatic As enlargement and infiltration occur manifestations of pressure and pain may develop and the syndrome of superior vena caval obstruction (q v) is not infrequently observed

Treatment of Mediastinal Tumors Benign mediastinal neoplasms cannot be differentiated accurately by clinical and radiographic methods from localized malignant forms Therefore the indicated therapy is surgical exploration and excision unless there exists some compelling reason to the contrary such as extreme old age or coexisting disease which itself has a lethal prognosis

The most useful exploratory incision is a long posterolateral one with rib resection since technical problems may be considerable Certain anterior tumors can be reached by medium sternotomy or parasternal chondrectomy Ideally the tumor should be totally extirpated in a single stage Certain large and infected cystic tumors in poor risk patients may be marsupialized for drainage and resected at a later date

The mortality rate for excision of benign and localized malignant mediastinal tumors is less than 5 per cent and in some reported series approaches zero

Invasive malignant neoplasms can only be biopsied or partially resected An attempt should be made to recognize these unfavorable cases by careful physical examination and to obtain tissue for microscopic study by simple techniques such as needle biopsy and the like When these fail a mediastinotomy may be required It is important not to treat a suspected lymphoma or other mediastinal neoplasm by radiation until a tissue diagnosis is established There are many pitfalls in so-called diagnostic radiotherapy

Hodgkin s disease confined to a local area should be treated with heavy doses of radiation and in a rare case this may be combined with surgical excision Widely disseminated tumors must be palliated with smaller doses of roentgen rays and such chemotherapeutic agents as the nitrogen mustards

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235 DISEASES OF THE PLEURA

John S Chapman

Upon being confronted by a complaint of chest pain one s first consideration must be to determine if that pain arises as a result of pleural disease In the differential diagnosis one must exclude disease of the heart and great vessels the esophagus the chest wall the spine the spinal cord the intercostal nerves and the abdominal viscera while at the same time one must be familiar enough with reference of pain (see Chap 4) to appreciate that pleural pain may be referred to the abdomen or that it may radiate to the neck (diaphragmatic pleurisy) In addition to eliciting a careful description of the pain one must be diligent in examination of the chest wall its muscles and bones Quite frequently the pain of fractured rib particularly if it occurs as a result of hard and chronic cough is indistinguishable from pleurisy unless one exerts a springing pressure upon the sternum which results in instant severe sharply localized pain Similar maneuvers will elicit the pain that results from separation of the costal cartilage from rib a condition in which radiography is of no advantage Careful palpation elicits a point localization and may reveal offset or fusiform swelling at the costochondral junction

INFLAMMATION OF THE PLEURA

Pleuritis is rarely a primary disease but results from extension of infection from contiguous areas The most direct source obviously is the lung and inflammation of the pleura is common in such diseases as the various bacterial pneumonias abscess

prolonged medical therapy or comparatively early decortication (i e as soon as the active inflammation has subsided) In these refractory inflammations the use of streptokinase and streptodornase may be undertaken Their administration is usually followed shortly by high fever and perhaps a rapid increase in the amount of fluid in the pleural cavity For this reason an intercostal catheter is frequently introduced into a previously determined pleural pocket and the enzymes introduced through the catheter which is then clamped for 12 hr At the end of the period it is unclamped and connected with an underwater seal to a drainage bottle The procedure may be repeated in 3 or 4 days

If marked reexpansion of the lung does not occur within 2 weeks of such treatment the catheter should be removed and the process allowed to proceed to its natural culmination Although many patients at this point may present very disappointing radiographic results considerable clearing may take place slowly over a period of several months Surgical decortication may then be considered in the light of the remaining pleural masses and the effect of the disease process on pulmonary function

The presence of a pleural fluid level in chest films indicates the presence of both fluid and air and establishes bronchial pulmonary or esophageal communication with the pleura An open bronchopleural fistula should be considered in every case and at the first aspiration of fluid 1 ml of methylene blue should be injected into the pleura but no other substance If blue dye appears in the sputum (occasionally it is necessary to bring out the blue color by means of hydrogen peroxide) open surgical drainage becomes an emergency measure And as long as any possibility of fistula exists no fluid of any sort should be injected into the pleural space but rather the sac should be kept as nearly dry as possible and the patient urged to lie on his affected side

PNEUMOTHORAX AND HEMOPNEUMOTHORAX

Pneumothorax Spontaneous pneumothorax may be either primary or secondary to some evident disease of the lung When obvious cause is apparent on physical roentgenographic or laboratory examination it is usually either tuberculosis abscess or carcinoma but occasionally generalized bullous emphysema is the causative disease In all these instances the problem is much graver than in primary spontaneous pneumothorax not only because of the gravity of the underlying disease but also by reason of the strong probability that the opening through the pleura may persist that escape of air into the pleura may continue that infection is almost certain to occur and that as a result of all these facts the lung can be reexpanded only with the greatest difficulty The signs and symptoms are the same as those given below for uncomplicated primary spontaneous pneumothorax Treatment also is essentially the same as that given for the primary condition except that in these instances large doses of antibiotics are strongly indicated For consideration of tuberculous spontaneous pneumothorax with empyema and persistent bronchopleural fistula see Chap 141 Particularly in the case of putrid abscess with associated large empyema and patent bronchopleural fistula there is urgent need of open surgical drainage to manage both the abscess and the empyema as well as to prevent spill over into healthy lung tissue

The cause of primary spontaneous pneumothorax is thought by most authorities to be the rupture of subpleural bullae or blebs The exact mechanism of rupture is not known but in most cases it is evidently not a result of exertion The bullae or blebs are believed to arise as a result of localized obstructive bronchitis and to constitute in fact very limited areas of emphysema If there is associated fever and formation of serofibrinous exudate there is reason to regard these pneumothoraxes as resulting from inapparent tuberculosis of the lung Other findings that are regarded as being indicative of tuberculosis are numerous apical adhesions though this rule is by no means infallible

The escape of gas into the pleural cavity usually is associated with marked pain which may be felt in any part of the chest on the affected side or referred to the neck or abdomen Such pain is aggravated by any physical exertion and mildly by respiration but the pain may increase rather steadily in the absence of physical activity As a rule when the patient is put to bed pain subsides within 24 to 48 hr after the onset Dyspnea develops early as a result of pain but becomes more intense later if the accumulation of pleural gas produces positive pressure (tension pneumothorax)

On examination the affected side appears full and motionless and it is especially noteworthy that expiratory motion is absent The percussion note is ringing and breath and voice sounds are reduced The trachea and heart will be shifted only in case of considerable pneumothorax Fluoroscopy and x ray reveal various degrees of pulmonary compression

The immediate treatment is bed rest plus relief of pain which frequently may require morphine (15 mg) though codeine (30 to 60 mg) or Demerol (100 mg) may be sufficient Some authorities start oxygen at once but this would not appear to be necessary unless cyanosis is present The reabsorption of nitrogen from the pleural cavity which results from inhalation of 100 per cent oxygen does not seem a sufficient justification for its use in the absence of cyanosis On occasion if the

white cells almost solely lymphocytes and with a number of red cells as well Such a fluid is produced most commonly by neoplastic or embolic disease

On rare occasions the inflammatory fluid usually a sequel of embolic or neoplastic disease or of mild trauma to the pleura may contain from 60 to 90 per cent eosinophils Experimental study suggests that such cells are late responses to the presence of blood certainly it is usually fruitless to search for a recognizable allergic or parasitic explanation

Noninflammatory Pleural Fluids On the basis of the strict definition set forth true transudate is to be found only in states of salt and water retention such as congestive heart failure or the nephrotic stage of renal diseases The only exception is the fluid *ex vacuo* which accumulates in a pleural sac when the intrapleural pressure reaches −20 cm H_2O and overcomes the oncotic pressure

Chylothorax a condition encountered very rarely is usually associated with neoplastic erosion of the thoracic duct The fluid aspirated is characteristically milky in appearance and shows microscopically great numbers of fat droplets

Huge numbers of cholesterol crystals may be found in pleural fluid which has lain neglected in the chest for many months The fluid is grossly quite cloudy and looks like white or cream colored pus Hardly any cells are to be found and most other studies are fruitless

The discovery of bile in pleural fluid is of very great importance and is a common finding in thoracoabdominal trauma Such fluid indicates a free communication between the liver parenchyma and the pleural cavity and calls for surgical measures

Physical examination of the chest in patients with noninflammatory fluid presents the same findings with the exception of tenderness that are obtained over inflammatory fluids The radiologic findings are also the same

In fluids which have been present for a very long time however there may be reduction in size of the chest and a shift of the mediastinum to the side of fluid The explanation of these observations is that the lung underneath the fluid has been markedly collapsed and has never been able to re expand even though a portion of fluid has been reabsorbed The findings are thus the same as those in fibrothorax the sole difference being the discovery of loculated fluid

Treatment of Pleural Effusion Attempt at aspiration is indicated whenever pleural fluid is suspected The three main objectives are (1) mechanical relief of dyspnea (2) reexpansion of lung and obliteration of pleural space in all inflammatory pleurisy (3) acquisition of information from the fluid and from complete visualization of the lung All three purposes demand complete emptying of the pleural sac Repeated taps are perfectly justifiable so long as they serve any one of the above purposes So long as one follows a careful technique with regard to asepsis is generous with local anesthetic agent and keeps the aspirating system closed to the atmosphere one need have little fear of accidents Lung laceration and the production of pneumothorax may be avoided by the use of an anchoring clamp on the needle advancement of which should be stopped the instant the pleura is traversed

Sterile tubes for bacteriologic study should be available and some should contain an anticoagulant since clotting may set in very rapidly and completely ruin the specimen for detailed study

The minimum examination of pleural fluid should include one s own gross observations as to color odor viscosity and turbidity specific gravity a total and differential cell count and protein determination In addition cultures for tubercle bacilli fungi or anaerobic organisms guinea pig inoculation and Papanicolaou or other cytologic study may be necessary When tuberculous pleurisy with effusion is to be considered a sugar determination may be of assistance Such effusions are said to contain relatively less sugar (compared to the blood) than do other fluids Personal experience suggests that the study is of very limited value

The differential diagnosis may remain in doubt after all these procedures If the fluid is inflammatory and not otherwise explained the tendency in the past has been to regard such effusions as tuberculous till proved not to be In some cases much time and trouble may be saved for the patient with obscure effusions if decision on pleural biopsy is reached early

The treatment of pleurisy is the treatment of the fundamental disease for which unfortunately in many instances there is no specific therapy In such cases the problem resolves into one of relieving the patient s dyspnea by repeated taps When the etiologic agent is bacterial however the effusion is commonly treated by aspiration of the pleural contents and administration of antibiotics Direct injection of antibiotics into the pleural cavity apparently is not always desirable though in heavily contaminated pleurae the injection of 200 000 units of penicillin daily or every other day may be of some assistance In early pneumonias with serofibrinous effusion results are usually highly satisfactory

If fluid develops in the face of inadequate or inappropriate antibiotic therapy the course is likely to be much more prolonged and the results are less satisfactory In such cases loculation develops large masses of fibrin are laid down and aspiration usually is productive of only a few milliliters of fluid Under these circumstances the choice lies between

result of congestive heart failure (see Chaps 14 26) Congenital anomalies of the heart and great vessels rarely if ever produce direct effects upon the pulmonary parenchyma although aneurysm of the aorta frequently may produce bronchial obstruction with consequent diffuse infiltration and suppuration (see below) In extensive roentgenographic surveys aneurysm of the pulmonary artery is encountered occasionally the condition is of interest chiefly from the fact that it must be differentiated from aortic aneurysm carcinoma of the bronchus and hilar adenopathies

PULMONARY EMBOLISM AND INFARCTION

In this discussion embolization will be used to refer to the passage through the circulation of any type of material foreign to the normal content of the vessels The commoner materials are blood clot marrow fat or gases Occasionally as in wounds from missiles metallic foreign objects may enter the circulation and be carried centrally

Infarction refers to damage to the structure of the lung itself Hence it is possible for embolization to occur without infarction but not for infarction to take place without an embolus

Embolization of the pulmonary circulation with fat takes place frequently as a result of severe injury especially to the lower extremities pelvis and spine Embolization by clot is a common complication in patients recovering from surgical operations severe injury to the legs prolonged febrile illnesses and in patients with cardiac disease The commonest source is the veins of the calves but emboli may arise from the pelvic veins or in patients with atrial fibrillation from the right atrium Gas embolization of the pulmonary circuit undoubtedly occurs with some frequency during intravenous fluid administration in traumatic or surgical opening of vessels of the neck and as one aspect of caisson disease (see Chap 106) In the case of gas embolization the large pulmonary bed is usually able to accommodate considerable quantities of gas and aside from temporary breathlessness and a sense of oppression no serious damage occurs unless gas reaches the left side of the heart

Marrow fat and clot particles may be of any size from minute fragments to occlusive masses The symptoms depend largely on the size of the clot and perhaps on reflex changes produced in the pulmonary vascular bed In mild cases the patient may have episodes of dyspnea tachycardia and anxiety with retrosternal pain and sometimes with fleeting attacks of pleuritic pain for which no cause is evident The blood pressure may be quite variable with episodes of sudden fall corresponding to the occurrence of retrosternal pain or discomfort brief periods of a shocklike state may follow

Massive embolization may be preceded by such seemingly terminal symptoms or may take place without warning In severe embolization the patient who may previously have seemed quite well, suddenly experiences severe retrosternal pain becomes cyanotic and intensely dyspneic and develops vascular collapse Differentiation from occlusion of a coronary artery may be very difficult Death may occur within a few minutes If the patient survives the severe episode he may remain in a state of profound shock from which with appropriate treatment he may slowly recover If the treatment of pulmonary embolization is to be successful therapy must often be undertaken while the diagnosis is presumptive In some instances death takes place so rapidly and with so little warning that no therapy is possible If nonfatal shock occurs the treatment is like that of shock in association with coronary heart disease Results of attempts at embolectomy from the pulmonary artery have been such that the procedure is rarely undertaken Other treatment if the patient survives the acute episode is directed toward prevention of additional embolization if the site of origin can be identified and occluded from the main circulation

Pulmonary infarction is the pathologic change that may result from an embolus Castleman distinguishes true infarcts with necrosis from very similar changes of intense hemorrhage into tissue but without necrosis the latter he defines as *pseudoinfarcts* Clinically the conditions are not differentiable except when it is possible to discover radiographic rarefaction in the center of the opacified area

The infarcted area early presents grossly the appearance of red infarction and microscopically the appearance of necrosis Later the gross appearance is that of the so-called *white infarct* while still later it is possible that the most careful search of the lung will fail to show any residual damage as the complete dissection of the pulmonary arterial tree may show no evidence of clot or of recanalization

Infarction may succeed a clinical picture of embolism as described above or may (and more usually does) manifest itself as the sudden onset of severe pleuritic pain followed immediately by cough cyanosis and dyspnea and a little later by blood spitting On occasion there is a repetition of the attack, with pain in some other area of the same or the opposite side

Pleural pain is very common and usually quite severe If the pain has been at all striking or persistent the patient should be observed closely for evidence of pleural fluid

patient is in considerable distress and the pneumothorax is large and under positive pressure aspiration of air is indicated Although one may relieve a patient merely by syringe removal of gas the pneumothorax machine with its manometer is a more precise method It is preferable to remove only 200 to 300 ml of gas on each occasion and to remove it frequently rather than to attempt very extensive decompression since the rapid withdrawal of gas tends to reopen and perpetuate the pulmonary pleural communication In some few cases accumulation of gas is so rapid and distress so great that more heroic treatment is indicated In such cases a sterile 18 French urethral catheter may be inserted through the second anterior interspace and connected to a water trap Some prefer to treat all but the smallest pneumothorax in this manner Even in very severe cases this measure is usually followed by rapid reexpansion but in a rare instance the rupture may be so large as to require continuous suction by means of the Stedman pump In some few patients the recurrence of pneumothorax is so frequent and disabling as to call for surgical intervention which usually consists of the removal of the bulla bearing area if one is present and careful poudrage of the pleural surface Recurrences following such procedures have not been reported

Hemopneumothorax In about 1 out of 8 patients with spontaneous pneumothorax the onset of the collapse is associated with hemorrhage into the pleural cavity In these instances of spontaneous hemopneumothorax which supposedly occur on the same basis as simple pneumothorax the bleeding is assumed to result either from the avulsion of an adhesion from the substance of the rapidly collapsing lung or from accidental involvement of a pleural vessel in the rupture To the usual picture of spontaneous pneumothorax there are added in severe cases signs and symptoms suggesting acute blood loss In perhaps 10 per cent of hemopneumothoraxes bleeding may be extreme hence almost all the pathologic material available on spontaneous pneumothorax is derived from autopsies of individuals who bled to death

The physical findings are those of pneumothorax plus basal dullness X ray studies usually reveal rather extensive collapse with a fluid level on the affected side

The treatment indicated is that for spontaneous pneumothorax in general with additional management for shock and hemorrhage when indicated In the usual case bleeding decreases as the lung collapses farther down but sometimes it continues very actively necessitating transfusions As a rule blood and pleural fluid should be withdrawn within a day or two to prevent formation of clot or extensive deposition of fibrin on the visceral pleura In the more severely bleeding cases aspirations may be required almost hourly The medical management of such patients should be continued only long enough to prepare for open thoracotomy with direct control of bleeding

Tumors of the pleura are discussed on p 1400

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236 DISEASES PRIMARILY OF CIRCULATORY ORIGIN

John S Chapman

Active hyperemia is the result of almost any kind of infection while passive hyperemia is the

result of congestive heart failure (see Chaps 14 228) Congenital anomalies of the heart and great vessels rarely if ever produce direct effects upon the pulmonary parenchyma although aneurysm of the aorta frequently may produce bronchial obstruction with consequent diffuse infiltration and suppuration (see below) In extensive roentgenographic surveys aneurysm of the pulmonary artery is encountered occasionally the condition is of interest chiefly from the fact that it must be differentiated from aortic aneurysm carcinoma of the bronchus and hilar adenopathies

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Marrow fat and clot particles may be of any size from minute fragments to occlusive masses The symptoms depend largely on the size of the clot and perhaps on reflex changes produced in the pulmonary vascular bed In mild cases the patient may have episodes of dyspnea tachycardia and anxiety with retrosternal pain and sometimes with fleeting attacks of pleuritic pain for which no cause is evident The blood pressure may be quite variable with episodes of sudden fall corresponding to the occurrence of retrosternal pain or discomfort brief periods of a shocklike state may follow

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Pleural pain is very common and usually quite severe If the pain has been at all striking or persistent the patient should be observed closely for evidence of pleural fluid

Hemoptysis varies in amount but is usually not over 100 ml on any occasion Frequently it is much less The first blood expectorated is usually bright red and not unlike brick dust sputum After a day or two the color of the blood gradually changes to dark red or to brownish black or may consist of small dark clots The duration of blood spitting may be for several days depending upon the size and number of infarcts Hemoptysis of any type however occurs in only about 50 per cent of all cases

The temperature rises within a matter of hours after the infarction The level of pyrexia frequently is not very high rarely exceeding 101 5 F and often not above 100 F The duration regardless of treatment with antimicrobial agents usually is 4 to 5 days with defervescence by lysis unless there is complicating pleural effusion or repeated infarction or unless the emboli are mycotic and part of a picture of severe generalized infection

Physical findings on examination of the chest of patients with pulmonary infarction are variable In the case of quite large infarcts one encounters dullness bronchial breath sounds increased voice sounds and numerous medium moist rales In other cases particularly where there are numerous small infarcts there may be suppression of the voice and breath sounds with rales or occasionally large rhonchi In still others if the infarcts are small and not numerous discovery upon physical examination is unlikely If effusion into the pleural cavity occurs the signs are those of any pleurisy with effusion flatness absence of the breath and voice sounds and diminished fremitus

When suspicion of pulmonary infarction exists careful examination of the legs may lead to the establishment of correct diagnosis (see below)

Leukocytosis as a rule is not high the count rarely passing 12 000 to 14 000 and left shift is only moderate Icterus may be present if hepatic function is impaired but in other cases one can find confirmation of the suspected infarction in elevated urine urobilinogen When fluid can be aspirated sterile blood fluid of fairly high specific gravity (1 014 to 1 018) with a relative paucity of white cells affords good confirmation of one s suspicion

The electrocardiographic finding of acute cor pulmonale with typical S_1–Q_3 configuration is rather unusual and among cardiac patients may be entirely concealed by other abnormalities

The x ray findings in infarction of the lung are by no means so simple as the classic description of a wedge shaped shadow with the base at the periphery An infarct may have almost any shape and rarely presents a triangular shadow in the normal posteroanterior projection The base of the infarct may be against any surface of the pleura including the diaphragmatic and the septal surfaces so that the normal chest film reveals any shape that may result from the passage of a plane through a cone A striking characteristic of the radiographic shadow is that almost always there is a clear zone of aerated lung between the peripheral density of the infarct and the hilum

If infarcts are multiple one may gain from the film a clue in the predilection of infarcts for the left lower lobe—a result of the comparatively straight course of the pulmonary artery to that portion of the lung

In successive films over a period of 5 to 10 days sometimes in much less time the original patchy infiltrations disappear and are replaced by irregular linear shadows which differ from plate atelectases in that they take various angles to the diaphragm rather than the horizontal lines of compression atelectasis

While smaller densities are usually of brief duration larger shadows especially if they are associated with congestive heart failure may persist for many weeks

In the rare case the center of the density undergoes rarefaction and the radiographic appearance is that of an abscess cavity with fairly thick walls The location is not that of the usual anaerobic abscess and air fluid level is not present Such shadows disappear almost as rapidly as do the non cavernous densities and leave no visible abnormality in the area of damage

The differential diagnosis of pulmonary infarction varies chiefly with the type of x ray shadow encountered If the shadow is large and single bacterial pneumonia presents the chief problem A very careful history is of the utmost value Infarction is striking in the development of pleuritic pain *prior* to the onset of fever whereas in pneumonia fever cough and dyspnea usually precede the onset of chest pain Pneumonia may be associated with a chill infarction is not Fever and leukocytosis are not often as high in pulmonary infarction as in the usual case of pneumococcal pneumonia In infarction there is no response of fever to antimicrobial therapy and tachycardia anxiety shock and cyanosis may be out of proportion to the visible pulmonary disease

A smaller infiltration may resemble primary atypical pneumonia but will differ in that infarction practically always produces sharp pleuritic pain and some degree of polymorphonuclear leukocytosis whereas such changes should not occur in atypical pneumonia

Infarction with cavity formation differs from abscess in mode of onset in absence of previous history of loss of consciousness in absence of foul

or purulent sputum in failure to respond to anti microbial drugs and in persistence of sputum that is chiefly blood either fresh or hemolyzed

Multiple infarctions may be confused with bronchopneumonia especially when they occur as a result of heart failure extensive trauma or prolonged infectious disease The problem is even more difficult in the presence of congestive heart failure with edema fluid in the pleural sac since infarction then takes place without pain A rise of temperature and the presence of leukocytosis are common to both diseases In neither case may there be pro ductive cough The development of an elevated serum bilirubin irregular bouts of tachycardia not otherwise explained and the appearance of red and white blood cells in pleural fluid that is sterile are points in favor of pulmonary infarction Pulmonary infarction especially if multiple or repeated delays or prevents response to usual management of congestive failure

Infarcts resulting from *fat emboli* differ in no respect clinically or radiographically from thrombotic emboli They should be suspected in patients who have recently experienced serious trauma to the spine pelvis or lower extremities and in whom dyspnea pleuritic pain cyanosis or unexplained shock is present The suspicion may be confirmed by the discovery of free or phagocytized fat droplets in the sputum (best seen in wet mounts or with Sudan III stain) provided there has been no recent ingestion of fat or possible cause for lipid pneumonia Similar fat droplets are often present in the urine

Mycotic emboli produce multiple abscesses of the lung The patient is severely ill with usual evidence of severe sepsis in addition to which there is marked dyspnea pleuritic pain cyanosis and sometimes shock Chest films reveal multiple abscesses distributed at random throughout both lungs Blood cultures should be positive The usual source of septic emboli is a gravid uterus on which a mechanical attempt at abortion has been made Severely traumatized and heavily infected extremities may be an occasional source of infected emboli

Treatment The treatment of pulmonary infarction is the treatment of the phlebothrombosis or thrombophlebitis which produces it Although penicillin is frequently prescribed on the basis that it may prevent infection in the damaged lung there is no real evidence that the antibiotic is of value Whether the administration of anticoagulants has direct effect upon the infarct itself is moot the duration of x ray shadows of infarction is so variable that demonstration of such an effect would be most difficult Hemoptysis is not of sufficient moment to call for any special treatment other than reassurance Pleural effusions if present should be aspirated since they may be of diagnostic value and particularly since they contribute to dyspnea

In the special case of septic infarction antimicrobial drugs of course are imperative Their choice will depend upon the antibiotic susceptibility of organisms obtained from blood culture While awaiting these results the physician should administer penicillin intravenously in the amount of 20 million units daily with 4 Gm of a broad spectrum antibiotic such as tetracycline Oxygen and fluids are demanded If the patient can be brought into condition that permits there is absolute indication for ligation of the inferior vena cava

Late Results Although in most cases of pulmonary infarction no serious damage seems to result in a certain number of patients a large embolus in a major artery may remain *in situ* and undergo propagation in the pulmonary vascular bed while repeated embolization by small clots may produce progressive vascular disease In either case the end result will be increasing and pulmonary arterial pressure with eventual right heart failure and death (see cor pulmonale)

PULMONARY HEMOSIDEROSIS

On occasion in patients with mitral stenosis with long standing congestive heart failure the chest film may reveal well defined miliary nodulation which has been shown pathologically to be deposits of hemosiderin with associated pulmonary fibrosis Whether lung function is significantly impaired by these changes is not known since pulmonary congestion from the stenosis itself as well as pulmonary arteriolar disease plays so large a part in the production of dyspnea in these patients

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237 DISEASES OF THE BRONCHI AND PULMONARY PARENCHYMA

John S Chapman

Certain of the more important specific infections of the lungs such as tuberculosis and the pneumonias have been discussed in preceding chapters For the sake of convenience the various neoplastic disorders of the respiratory system are considered in Chap 238 The discussion to follow will be concerned with the remaining disorders of the lungs and bronchi

ACUTE BRONCHITIS

Bronchitis may occur as a primary disease may develop in the course of other specific infectious diseases or may occur as a result of distal pulmonary involvement Commonly the distribution is diffuse but occasionally it is localized

Among the specific infectious diseases in which bronchitis is a prominent phenomenon are pertussis influenza typhoid fever and the exanthemas but bronchial irritation has also been reported in malaria some of the rickettsial diseases and in those worm infestations marked by a pulmonary phase Localized bronchitis is found in the bronchus draining suppurative parenchymal disease and areas of tuberculosis or subjected to extrinsic pressure

In many individuals almost every invasion by the common cold results in a descending infection which eventually produces an acute inflammation of the trachea and bronchi The disease is usually mild and tends to run its course within one or two weeks

Such gases as were used in the First World War produced intense bronchial irritation which in severe cases went on to pneumonia or pulmonary edema Under industrial conditions exposure to these gases may develop on occasion from this standpoint the most important are ammonia chlorine sulfur dioxide hydrogen sulfide and under special conditions phosgene It is conceivable that severe exposure may result occasionally in emphysema

In *acute bronchitis* the complaints are those of cough expectoration at first of scanty mucus later of more abundant mucopurulent material and very commonly a sense of rawness located behind the sternum and extending somewhat to either side The patient states that cough is associated with tearing pain located in the same areas The temperature is variably elevated more commonly only mildly but occasionally to as much as 103 F

Physical examination reveals mild to severe acute illness in a patient with racking dry cough In the usual case there is injection and edema of the nasal and pharyngeal mucous membranes Unless the bronchitis is superimposed on some chronic disease the examination of the chest is noteworthy only for variable large rhonchi and occasional inspiratory fine wheezes

X ray of the lungs reveals no evidence of disease and laboratory studies commonly present the positive findings of moderately elevated white blood count with some increase in polymorphonuclears and a mild left shift Sputum usually contains a variety of common inhabitants of the respiratory tract with gram positive cocci in the great majority Other laboratory studies are of no value except for the exclusion of bronchitides associated with typhoid fever and the other specific infectious diseases

Treatment should consist primarily of bed rest Treatment is symptomatic Steam inhalation will control moderate cough but codeine may be required Salicylates are useful for fever or malaise

CHRONIC BRONCHITIS

In a certain percentage of patients cough and expectoration persist sometimes for many months In the early mornings the cough is usually productive but it frequently occurs during the night in paroxysmal form with little or no sputum Sometimes frank hemoptysis may occur but more usually the patient complains only of blood streaked sputum Pain is not a prominent feature in such illness and there is no fever weight loss or decline in strength or vigor Of this group a large number have additional complaints referable to the nose or paranasal sinuses and postnasal drip is very common Mouth breathing may contribute to difficulties while persistent cough itself adds to bronchial irritation and edema A personal or familial history of allergy is usually lacking but the history of smoking is almost always present

Examination usually reveals a somewhat hyperemic but frequently crusted and dry nasal mucosa The pharynx either is of a "granular" or lymphoid character or presents the appearance of unusual dry redness The physical examination of the lungs presents nothing more than occasional rhonchi or a rare inspiratory wheeze No changes in the circulatory status are evident and there is no clubbing of the fingers

The chest film is normal in appearance and the blood count not remarkable Sputum as a rule is rather scanty and is composed of tenacious mucus in which there are relatively few cells or organisms Films of the sinuses frequently present no evidence of disease

The differential diagnosis in such individuals is of considerable importance since neither the negative chest film nor physical examination can be considered sufficient to exclude more serious disease In a certain number of cases tuberculosis first manifests itself in such fashion so that the sputum must be carefully searched and cultured to exclude that disease Carcinoma of the bronchus and bronchiectasis constitute other possibilities that need to be absolutely excluded therefore these patients may often require bronchoscopy and bronchography before one can conscientiously reassure them completely

At bronchoscopy the mucosa of the trachea and bronchi appears usually red and somewhat redundant and has a tendency to stick to the instrument Coughing is usually marked during bronchoscopy of such patients and it may be observed that the walls of the trachea and bronchi almost collapse shut during cough Secretions are usually very scanty Rarely is it possible to find ulceration or definite granulation Biopsy if taken reveals only chronic inflammation

Bronchograms commonly reveal a loss of finer branches with much beading (due to droplets of mucus) along the larger branches Mild degrees of cylindric bronchiectasis sometimes are observed

The first step in treatment consists of the exclusion of any possible irritants Tobacco is interdicted If the patient s occupation brings him into contact with dust fumes gases or paint in many cases he will never get rid of his cough until his environment has been changed He should avoid public gatherings and should attempt to maintain both his house and his place of work as thermo stable as is possible Usually some degree of humidification of the air particularly in winter is required Moderate exercise in the open has seemed of some value as has much outdoor activity in the sun during the summer

For immediate symptoms a codeine-containing cough syrup and a steam kettle afford about as much relief as can be obtained Particularly when sputum is scanty and tenacious the addition of potassium iodide or ammonium chloride may be of some benefit In certain patients the antihistaminic drugs may offer additional relief These things failing one may try a large number of expedients usually with little success Occasionally a patient recovers entirely following diagnostic bronchoscopy Not infrequently one may have to prescribe residence in a climate warm sunny and dry throughout the year

PULMONARY FIBROSIS AND EMPHYSEMA

Under this combined term are grouped a large number of somewhat related conditions One or the other element of fibrosis or of emphysema may predominate but one element is practically never found without some trace of the other The clinical disease may be defined as a chronic respiratory process characterized by some type of respiratory insufficiency (ventilatory or alveolocapillary) and marked by various degrees of overdistention of the alveoli interspersed among areas of fibrosis

Classification

Classification of these diseases on a basis of pathologic and physiologic differences seems sound Three types are recognized The first is diffuse obstructive emphysema with characteristic overdistention and bulla formation The second perifocal emphysema develops about foci of fibrosis and is associated with comparatively mild overdistention The third variety is senile emphysema

Any of these types except senile emphysema may be either localized or generalized Obstructive emphysema may be confined to a single segment or it may involve homologous segments on the two sides with marked compression of the remaining segments

Pathology *Bullous Emphysema* Grossly the lungs are greatly overdistended rather pale noncollapsible and feathery to the touch Over the surface but particularly along the margins large air containing vesicles are frequent On section numerous air vesicles ranging in size from 2 mm to several centimeters in diameter are seen throughout the entire lung substance Very little normally crepitating tissue can be found

The histologic picture is that of flattening of alveolar septa rupture of alveoli into each other obliteration of blood and lymph channels and in the interstitial tissue a round cell infiltration with areas of true hyaline fibrous tissue The bronchioles and bronchi usually reveal thickening of the mucous membrane with submucosal round cell and polymorphonuclear infiltration

Small Lung or Senile Emphysema The lungs usually fail to collapse when the chest is opened and occasionally bullae are seen along the margins The lungs are flabby and distinctly less elastic than normal On section vesicle formation is minor and relatively few bullae are seen

Histologic examination is likely to show very minor changes

Pathogenesis Various explanations of diffuse obstructive emphysema have been offered By certain writers it is considered to be the effect of atrophy resulting from vascular changes by others to result from some type of congenital defect in supporting and elastic tissues by the majority to develop as a consequence of chronic bronchitis

Once the process has begun the steps in its progression are obvious Submucosal swelling and

readily demonstrable bronchospasm result in trapping of air since bronchiolar lumens narrow during expiration and diseased branches may close entirely Alveoli overdistend and eventually rupture into each other Since even the major bronchi collapse during hard cough stasis of secretions develops and adds to the bronchitis present Rapid changes in pressure as a result of cough tend further to overinflate distended areas which in turn compress adjacent healthy alveoli

Perifocal emphysema is thought to develop about small areas of nodular fibrosis such as a healing nodule of tuberculosis If the disease is generalized the exciting cause may be some diffuse disease such as healed sarcoidosis Bronchitis is not a factor but the condition seems to result in distortion of respiratory bronchioles Ventilatory defect is chiefly of the restrictive type

The pathogenesis of small lung emphysema is thought to be mainly the process of aging with gradual degeneration of the elastic fibrils in the interstitial tissue of the lung Another important factor in the production of this disease is the calcification of the costal cartilages and variable ankylosis about the heads of the ribs so that thoracic wall motion is greatly reduced Postural changes that go with age tend to inhibit the free motion of the diaphragm

Pathologic Physiology *Bullous Emphysema* If one bears in mind that expiratory obstruction is fundamental in the large lung type of emphysema the physiologic changes that result are obvious The first effect is retention of gas in the lungs In physiologic terms this means that the functional residual volume is greatly increased Most of this increase is in the form of true residual volume for usually expiratory reserve volumes are reduced below normal values The effect of an increase in functional residual volume is to displace all other volumes so that the patient comes to breathe nearer and nearer to the top of his pulmonary capacity Tidal air nearly always is increased and the inspiratory capacity can only be markedly decreased since the total lung volume is almost constant for the same individual if there is no progressive fibrosis

If functional residual volume is increased and expiration is obstructed a necessary consequence is retention of carbon dioxide The first effect of increased concentrations of this gas will be a drive toward more rapid and deeper respiration and therefore a larger tidal air volume But because of the degree of bronchospasm in different areas of the lung diffusion of gases is inefficient and trapping in first one area and then another takes place readily Thus another of the major factors in the physiology of emphysema is poor mixing of gases As the carbon dioxide tension of alveolar air (and hence of arterial blood) rises the respiratory center tends to become relatively refractory to the carbon dioxide stimulus to respiration and the patient comes to breathe largely from the hypoxic stimulus

Carbon dioxide retention sets in motion a series of chemical changes in the blood The immediate effect is respiratory acidosis which the body at once undertakes to compensate Compensated gaseous acidosis is achieved by increasing the alkali reserve (carbon dioxide–combining power) which is accomplished by excretion of chloride The chemical picture of the individual with advanced emphysema is therefore one of decreased chlorides increased alkali reserve and—as long as the gaseous acidosis is compensated—a normal or but very slightly lowered pH Other chemical aspects of the disease are elevated carbon dioxide tension and content of alveolar gas and arterial blood with near normal oxygen content and tension except under conditions of exercise or advanced disease when unsaturation may occur

From the ventilatory standpoint the picture in sum is that of increased tidal volume with hyperventilation reduced expiratory reserve volume poor mixing trapping of air with delayed emptying a moderately reduced vital capacity and a markedly reduced maximal breathing capacity and respiratory reserve Expiratory flow rate is slow and lung compliance reduced

Circulatory effects are to be expected if the respiratory system is so severely affected but a good many patients die of emphysema without ever having manifested circulatory failure When the circulation is involved however several factors play a part If hypoxia is fairly marked and persistent secondary polycythemia may develop with increased hematocrit and blood viscosity If hypoxic spasm or obliteration of the pulmonary capillary bed develops pulmonary hypertension is certain to result and consequently right ventricular dilatation and hypertrophy with ultimate right heart failure

A secondary effect on the circulation results from the prolonged forcible expiration The intrathoracic pressure is raised and blood is held out of the thorax When inspiration commences a large increment of blood enters fills the right atrium and ventricle and is then ejected into the pulmonary circuit The effect is of phasic alteration in cardiac output manifest peripherally as a paradoxic pulse and centrally as cyclic variation in pressures

The mechanical work of respiration in patients with obstructive emphysema is much increased since expiration has to be aided by active contraction of accessory respiratory muscle The problem of fatigue should be borne in mind when these patients are placed under stress Decreased clim

ination of carbon dioxide with decompensated gaseous acidosis may result from administration of oxygen or anesthetic agents

Perifocal Emphysema If the disease is limited in extent there is likely to be no significant physiologic change If the process is extensive ventilatory insufficiency may be of the restrictive type Trapping is usually not sufficient to result in carbon dioxide retention but fibrosis may affect the capillary bed either to result in physiologic shunts obstruction of the vascular bed or diffusional defect The major chemical changes will be reduction of arterial oxygen content pressure and saturation and if hyperventilation occurs decreased arterial carbon dioxide with potential elevation of pH

Small Lung Emphysema The major findings in this disease are those of reduced vital capacity maximal breathing capacity and breathing reserve Residual volume and functional residual volume may be mildly to moderately increased Since bronchial obstruction is not a significant feature of the disease there is no carbon dioxide retention and consequently none of the secondary chemical alterations Secondary circulatory effects are usually absent

Contributing Factors Bullous emphysema is predominantly a disease of males In a fairly large series the age at onset was frequently in the late thirties or early forties and in a significant number the disease was stated to have followed a specific attack of respiratory infection Cases were equally divided among people of sedentary occupation and those who performed moderate to heavy manual labor Many patients gave histories suggesting unusual vigor in their earlier lives and almost all had been heavy smokers Nasal disease under various appellations was conspicuous in the history of over half

Senile emphysema appears more equally in the sexes although again there is male preponderance Aging appears to be the only factor of great importance though posture and a previously sedentary life may play a small part in the inefficiency of ventilation and the fixation of the thoracic cage

It is very important to point out that the patient s age is not sufficient grounds for attributing breathing difficulty to senile emphysema Quite elderly men may have bullous emphysema and occasionally younger individuals develop the senile type

Finally emphysema must be understood to occur either alone or as a complication of other pulmonary diseases True pathologic emphysema may develop in association with tuberculosis pneumoconioses bronchiectasis and chronic abscess Equally any of these diseases as well as carcinoma may develop in any individual who already has bullous emphysema In such instances it is most important to determine that the condition present is emphysema rather than simple over distention a condition in which the lung or lobe is larger than normal but functions quite well without air trapping irregular mixing or carbon dioxide retention

Symptoms The first complaint is either of shortness of breath or of cough Shortness of breath is likely to be noticeable upon any exertion to be aggravated by changes in weather or by excitement and to be markedly increased by upper respiratory infection The patient is quite comfortable when recumbent but frequently states that he is unable to lie on either side Cough is usual and it may be nonproductive or moderately productive Paroxysms of cough particularly early in the morning are exceedingly troublesome and changes in posture nearly always result in difficult breathing and in increased cough Sputum is usually rather tough tenacious and mucoid but may be mucopurulent from time to time Not infrequently bloody streaks and small hemoptyses may be noted Chest pain particularly in the lower costal areas occurs rather often and is of a definitely pleuritic type Examination may reveal a fractured rib from cough

As the disease progresses it is usual for rather marked loss of weight to occur Patients may be so dyspneic as to be unable to eat with any comfort since swallowing demands inhibition of respiration Swelling of the feet and ankles indicates a rather late stage of the disease with onset of right heart failure

The symptoms of senile emphysema as a rule are quite mild and consist chiefly of shortness of breath upon exertion Cough is mild and other symptoms are usually absent except perhaps for some complaint of weakness and fatigue The symptoms of perifocal emphysema are shortness of breath and later those of cor pulmonale

Diagnosis *Physical Examination* Early emphysema may be so mild as to be detectable only by rather extensive pulmonary function tests The average patient with sufficient symptoms to call for medical aid will therefore be described The patient is usually in obvious respiratory distress and often can speak but a few words at a time There may be a trace of cyanosis about the lips and nails Neck veins frequently are engorged during the rather long expiration

Characteristically the chest is large and deep with elevation of the clavicles so that the neck appears unduly short High dorsal kyphosis *is nearly* always manifest The costal margins flare outward and the maximal respiratory excursion *is seen in* the midepigastrium where cardiac pulsation also is

visible and often quite forceful Chest wall motion is very limited and is restricted to a lifting upward and forward of the sternum Expiration is prolonged and is accompanied by obvious effort In certain patients the epigastrium bulges outward during expiration and retracts during inspiration a finding that indicates a marked incoordination of respiratory muscles as well as practically total lack of function of the diaphragm

Percussion produces a ringing hyperresonant note The heart margins are difficult to percuss and the diaphragm is very low Often there is no change in position of the diaphragm from inspiration to expiration

On auscultation the heart sounds are usually distant or inaudible If they can be heard P_2 is often much greater than A_2 and may be reduplicated Breath sounds are very distant throughout the chest except when emphysema is limited for example to the upper lobes in which case the breath sounds above are very distant while below breath sounds may be quite harsh When the sounds have sufficient volume to be followed throughout the phases of respiration it is noteworthy that they take on a distant bronchovesicular character due to the patient s obstructed expiration Adventitious sounds consist primarily of variable wheezes and rhonchi which may be heard during both phases of respiration It is characteristic that they are variable in size in time and in position Now and again one may hear along the lower borders of the axillae very fine crackling sounds similar to very fine moist rales These are thought to be the result of crepitus produced by the movement of vesicles across the pleura

Patients with senile emphysema present relative fixation of the chest poor motion of the somewhat depressed diaphragm but breath sounds that are usually fairly clear and possibly harsh Adventitious sounds are rarely heard and the physical examination of the heart is as satisfactory as in the normal individual

In perifocal emphysema only tachycardia hyperventilation and possibly cyanosis may be found

Roentgenographic Findings The ribs usually appear to be in an elevated and nearly horizontal position and the interspaces are widened The diaphragm can be seen at the level of the eleventh rib or just below it and characteristically the upper surface of the diaphragm appears to be scalloped with numerous arcs that are concave upward The mediastinum is usually in the normal position but the heart appears to be small because of the fact that the apex is rotated downward Roentgen signs of right ventricular enlargement or increase in size of the pulmonary outflow tract are seen only occasionally

The lung fields are remarkable for their radiolucency and for the absence of lung markings Occasionally one may see linear and patchy densities which represent areas of heavier fibrosis Sometimes it is possible to outline large bullae with very thin fibrous septums between adjacent ones If the fissure lines are visible they may be displaced somewhat from their normal positions depending upon the areas of maximal emphysema or fibrosis When emphysema is localized to a single lobe the other homolateral lobe may appear to be much reduced in size and to present the roentgenographic appearance of partial collapse Markedly asymmetrical emphysema may displace the heart and mediastinum to the opposite side and occasionally may simulate spontaneous pneumothorax very closely

It is noteworthy that in the lateral films the heart appears to be separated from the sternum by a considerable distance which is occupied by the bullous margins of the lungs Fluoroscopic examination presents a diaphragm that may move through not more than 2 to 3 cm from maximal inspiration to maximal expiration If the ascent is greater than that it is usually accomplished very slowly Lightening and darkening of the lung field as a whole does not occur during respiration but one may see portions of the lung darken with expiration while adjacent areas remain quite lucent This discovery is a certain sign of air trapping as is a shift of mediastinum out of the midline during expiration

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Laboratory The usual laboratory studies are of little value unless there is question of secondary polycythemia or some complicating disease Sputum smears and cultures present a variety of organisms none of which can be regarded as significant Minimal chemical study should include chlorides and carbon dioxide–combining power

The circulation time and venous pressure should be determined if there is any question of associated heart disease

Treatment Under ideal conditions the patient should live in a warm dry climate in which exposure to dust irritants pollens and smoke should be minimal if not completely absent His occupation should preferably be sedentary and he should be protected against emotional stress and any but the mildest exertion If his occupation permits he

should take a rest after lunch and have more than the usual amount of rest at night *During epidemics* of respiratory disease he should avoid all public gatherings *Tobacco should be completely forbidden* though occasional and moderate use of alcohol *is permissible If he is underweight* several small feedings of high caloric value rather than three *regular meals may be advised He must be made* to understand that his condition is not reversible but that *its progression* can be arrested and that his symptoms can be improved Some attention to the condition of the nasal mucosa may be indicated but extensive nasal surgery should be avoided if possible Frequently antihistamines suffice to control a chronic nasal irritation if cessation of smoking does not

Three general purposes are undertaken in the treatment of diffuse obstructive emphysema promotion of bronchial drainage control of bronchial infection and improvement in bronchospasm and bronchial *obstruction In practice* measures taken for one of these purposes to some extent aid in the others

Bronchodilators Parenteral adrenalin has little place except when emphysema is associated with true bronchial asthma Aminophylline is very useful This drug may be administered in doses of 0 25 to 0.5 Gm intravenously over a period of at least 5 *min as often as every 4 hr orally in maintenance* therapy in doses of 0 2 to 0 3 Gm either alone or in *combination with other drugs four times daily or* rectally as 0 3 to 0 5 Gm in solution introduced through a catheter well up in the rectum This method of rectal administration produces rapid relief and avoids the irritation produced by suppositories

Ephedrine as 15 to 24 mg tablets is convenient for the patient to carry about with him and gives some relief during working hours when he may wish not to use a nebulized bronchodilator This drug may be used as such or in combination with aminophylline in the form of many useful proprietary tablets or capsules

Nebulized bronchodilators are solutions of various derivatives of epinephrine or similar compounds *Those most in favor include* Isuprel Aerolone compound and Asthmanefrin They may be administered through *any nebulizer capable of producing* a finely divided aerosol Much better results follow inhalation of these mists after the patient makes a strong exhalation rather than as he attempts strong inspiratory efforts Such therapy may be used as often as once an hour

Antibiotic Therapy The interest in nebulized antibiotics has largely subsided If the sputum is purulent and voluminous repeated short (5 to 7 day) periods of penicillin treatment are quite beneficial The usual dose is 300 000 units daily For *prophylaxis Bicillin 1 million units monthly may* be tried but is of questionable value

In some patients maintenance protective therapy with a broad spectrum antibiotic 250 mg daily *throughout the season of respiratory infection* may be of a little value

Organisms identified from sputum cultures are extremely variable What part some of them play in the bronchitis associated with emphysema is not evident Far numbers of them are insusceptible to ordinary antibiotics and probably can be ignored in many instances *Candida* and unidentifiable molds have been noted they are of interest only by virtue of the fact that under broad spectrum antibiotic therapy the yeasts may overgrow the usual flora and give rise to major difficulty themselves

Vaccines seem to have little or no effect in average cases A very rare patient may show some improvement on vaccine treatment In the opinion of most writers stock vaccines are likely to be fully as effective as autogenous preparations

Bronchial Drainage Postural drainage of the kind usually prescribed in bronchiectasis is of no value unless there are areas of active infection such as associated pneumonia Patients with emphysema *may be unable to tolerate* positioning Regular rest and sleep prone on an inclined plane *headdown at about 15 is helpful if the patient* can tolerate the position The shift upward of abdominal contents *raises the diaphragm and may* over a time result in some improvement in its muscular tone and power

Expectorants occupy a very uncertain place in promotion of bronchial drainage One of the major features of the disease is tenacious and bubbly sputum Saturated solution of potassium iodide 10 to 15 drops four times daily may be worth trying Enteric coated tablets of ammonium chloride are usually of no avail since disintegration of the tablets in the bowel is very uncertain Smaller amounts of ammonium chloride in solution are fully as effective

Much *interest has developed* in the use of detergents as means of liquefying secretions and lowering *surface tension Although some* writers have found no significant advantage in the use of such materials when it is *desired to try them it is usual* either to utilize a dense mist in a tent or to combine a bronchodilator with a detergent 1 4 *and* to nebulize by some mechanical source of pressure 10 ml of this mixture as often as every 3 hr The patient during the process of inhaling the mixture should make strong expiratory efforts rather than efforts at deep inspiration The use of vaporized water either as steam or as cold vapor may be of some advantage

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tions Under conditions of bronchiectasis quite large communicating shunts may develop between pulmonary and bronchial arteries Immediately surrounding the saccules a polymorphonuclear infiltration is visible at some distance slides reveal round cell infiltration and young fibroblasts as well as much old hyalinized fibrous tissue

Since bronchi are much more easily obstructed when they are of small lumen the onset of bronchiectasis is often in infancy or childhood The aspiration of foreign bodies bronchopneumonia and bronchial occlusion associated with primary tuberculosis are frequently precipitating causes Occasionally the disease results from postoperative pneumonia or other bronchial obstruction in later life

There is commonly a *history* of repeated pneumonic episodes frequent colds general decline in health and strength intermittent low grade fever with sweating and above all persistent cough with expectoration One common feature of the history almost diagnostic in itself is the statement that cough develops upon lying down The sputum is described as abundant yellowish sometimes chunky and hard but by no means universally is foul Hemoptysis is quite frequent and at times may be severe Pleuritic chest pain often develops with each fresh infection but is usually not very severe

Physical Examination The patient often appears chronically ill In characteristic cases over the area of disease the examiner encounters mild lag dullness diminished breath and voice sounds and considerable numbers of variably sized moist rales In the rare instances of disease of the upper lobe only the sole physical sign may consist of moderate impairment of the percussion note In bronchiectasis limited to the middle lobe if much shrinkage of the diseased lobe has occurred there may be no physical signs at all The distribution of physical signs is usually lobar or segmental in character Clubbing of the fingers is usually pronounced

Roentgenogram of the chest sometimes appears entirely normal either because there is very little fibrosis or pneumonia or occasionally—and this is particularly true on the left—because the bronchiectatic lobe is so completely contracted as not to be visible in the routine projection In more characteristic instances heavy linear stranding is to be seen radiating downward and laterally from the hilum in a few cases the affected lobes may appear almost solid

Laboratory work is of little diagnostic advantage other than in the exclusion of tuberculosis The sputum characteristically purulent does not often settle out in the classic three layered form On slide and culture other than anaerobes no significant organisms . . .

The bronchoscope may reveal somewhat dilated and displaced orifices of the lower lobe with evidence of chronic inflammation and with abundant purulent secretion Bronchograms which should be used only for diagnosis and mapping should show complete outlining of the major branches of both lower lobes the middle lobe the lingular segment of the left upper and some of the branches of the right upper Several views are necessary for complete study including posteroanterior and lateral upon filling the first side and both oblique views The amount of oil used in filling both sides should not exceed 15 to 20 ml but it is preferable to study only one side at a time

The basic treatment is surgical extirpation of the diseased areas a procedure that can now be carried out with a mortality of not over 2 per cent Unfortunately either because of the extent or distribution of the disease or because of associated emphysema extrapulmonary disease or age a certain group of patients has to be classified as inoperable and treated medically For these patients the most that can be accomplished is amelioration of symptoms and prolongation of life

Postural drainage is the most important single measure in the management of inoperable bronchiectasis Four or five times daily and for 10 to 15 min at a time the patient should adopt the position in which experience shows he will have most profuse drainage and make persistent coughing and chest squeezing efforts Oftentimes the patient in attempting to avoid this somewhat unpleasant part of his daily routine will state that he does not cough at all during the time he is in drainage position but does produce sputum after assuming a more natural one This argument should not deter the physician from insisting upon continuation of postural drainage Persistent regular use of the measure may often reduce sputum production by as much as 75 to 80 per cent and commonly changes a putrid pus to an odorless one An additional aid is elevation of the foot of the bed so that gravitational drainage may take place through the night The inhalation of digestive enzymes (pancreatic dornase and trypsin) may assist in liquefaction and drainage but may lead to untoward reactions

Other than these measures those general rules set out for patients with chronic bronchitis are indicated In addition if the bronchiectatic patient s strength is at all depleted he should be ordered to rest 1 hr after lunch and to secure 9 or 10 hr of rest at night All patients should receive penicillin parenterally at the first sign of fresh infection The use of Bicillin once monthly on a prophylactic basis is of considerable advantage Other antibiotics may be of use in patients who are sensi... or who have organisms resistant to penicillin

Other methods of bronchial drainage will be discussed under the subject of acute respiratory insufficiency

Mechanical Measures The fundamental problem of course is to produce an easier and more effective expiration

Pneumoperitoneum may be given for the purpose of elevating the diaphragm reducing the resting lung volume and aiding in the evacuation of secretion In perhaps half the patients there appears to be slight to moderate short term benefit from this procedure Abdominal binders of various types have been tried over a considerable period of time They may be used alone or in conjunction with pneumoperitoneum but on the whole patients tolerate them poorly and eventually discard them

Breathing exercises are widely used If the patient s cooperation can be obtained for repeated and prolonged practice such exercises are of considerable value Indeed after a time patients tend to perform the exercises automatically with each expiration The fundamental part of the exercise consists of education to use the abdominal walls as an additional expiratory muscle The hands fix and compress the costal margins with each expiration while the patient makes a blowing effort through partly closed lips After a few moments of such respiration the patient experiences much relief and after a few periods of instruction adopts the practice as a part of his daily routine

If emphysema is limited in extent for example to a single lobe surgical extirpation usually results in marked improvement for a time Further observation is needed to determine whether such benefit is lasting

Acute Respiratory Insufficiency Various intercurrent diseases may produce acute respiratory failure in patients with emphysema Trauma surgical procedures but above all acute upper and lower respiratory infections frequently result in decompensation of the patient s gaseous acidosis Such individuals are cyanotic and stuporous If the patient is to survive heroic measures are required Tracheotomy which allows ready access to the bronchial tree for repeated bronchoscopy or catheter suction is necessary in many cases Oxygen is demanded but its use is fraught with grave danger In the stuporous or near stuporous patient the use of the tank respirator makes it possible to administer oxygen with much less danger Usually it is desirable to administer oxygen by means of a positive pressure machine which produces not only much better ventilation of the areas of air trapping but may also aid in carrying nebulized bronchodilators to more distal bronchioles Some respiratory machines of the positive pressure type have negative pressure phases which produce the effect of cough

If tank respirators are not available oxygen must be administered with extreme caution The patient by reason of obstruction already has a high carbon dioxide pressure for which he is unable to compensate The use of oxygen depresses respiration still further and may result in profound coma If no mechanical device is available manual aid to expiration will have to be used from time to time Oxygen should be administered for 15 min intervals and the patient returned to room air breathing for 10 min intervals If the condition is slightly less severe oxygen at a flow rate of 1 to 2 l per min administered by nasal catheter is safe If respiration is not depressed the rate may be increased 1 l per min each hour until a full flow of 8 to 10 l is reached

Aminophylline—0 5 Gm in 500 ml saline per hour —should be administered and penicillin 600 000 units or other antibiotics may be added when indicated to each bottle of fluid

Cor pulmonale may result from advanced emphysema or from disorders which cause extensive pulmonary fibrosis Its treatment is considered on p 1271

BRONCHIECTASIS

The pathogenesis of bronchiectasis as demonstrated by experiment and supported by clinical observations seems to be the development of a necrotizing bronchitis behind a bronchial obstruction Neither infection nor obstruction alone would seem to be adequate No specific organisms are involved although they are usually anaerobes nor is any specific type of obstruction necessary The dilating force as applied to the diseased bronchial wall is chiefly an external pull due to the negative intrapleural pressure Cough is apparently a result rather than a cause of dilatation

A special type of bronchiectasis that seen in infants with cystic fibrosis of the pancreas is thought to be due to a disorder of mucous glands such that the mucus secreted is extremely tenacious and thick Upper respiratory infections are common among such marasmic infants so that both the obstructive and infective elements are present Since most such infants die in early life the combination of pancreatic fibrosis and bronchiectasis is of interest primarily to pediatricians

Pathologically the diseased lung reveals markedly dilated bronchi between which there is fibrosis and chronic inflammation Distribution conforms to lobes or segments The cartilages are missing in many cases and *oftentimes no residue of the original* bronchial wall can be found In certain areas the walls may be composed of abundantly vascular granulation on a fibrous tissue base while numerous angiomatous capillaries may be seen in other sec

pected The dosage of penicillin recommended is from 10 to 20 million units intravenously daily until the temperature is normal and good clearing is obtained The course of disease should be followed with posteroanterior and lateral films of the chest at 3-day intervals during the first 2 weeks of treatment and thereafter at weekly intervals

The same treatment is applied to subacute or chronic abscesses the most common cause of which is likely to be inadequate early treatment and follow up The duration of treatment is necessarily longer and the results are less satisfactory In almost all such cases perhaps after as long as 4 to 6 weeks a stationary point with from small to large residue is reached The patient by that time is asymptomatic

The problem confronting the physician is whether or not the results—so far as the x ray findings are concerned—are acceptable permanently Frequently it is impossible to decide The problem can usually only be solved by allowing the patient full activity without drugs and following him at regular intervals A return of symptoms even though mild or the occurrence of hemoptysis is indication for resection of the residual lesions

BRONCHIAL OBSTRUCTION ("Atelectasis")

This particular terminology is used not only because the obstruction of the bronchus is the primary and important phenomenon and the change in the lung secondary but also because the lobe or segment beyond the bronchial block is not merely airless but is filled with secretions and bacteria Of much more import than the identification of bacteria beyond the block are the nature and duration of the obstruction itself The cause of the block may be within the bronchus when it may be a foreign body an inflammatory stricture an acute swelling a tumor or merely a mucous plug or extrinsic as in the case of aneurysm mediastinal adenopathy or extrinsic carcinoma Only that atelectasis which arises as a result of compression of the lung from without as by fluid or pneumothorax is relatively benign in character since only in that type is free bronchial drainage available In this instance the remedy of course is the removal of the material producing compression of the lung which upon reexpansion suffers no fibrosis or loss of function except as the pleura may stiffen or adhere

Bronchial obstruction may be recognized by the presence of a lag upon inspiration a decrease in the size of the hemithorax a shift of the mediastinum and trachea to the affected side and elevation of the diaphragm of that side In the acute and earliest stages such as immediately postoperatively there has not been time for solidification of the obstructed segment and dullness is not encountered Breath sounds in such instances however will be diminished and large bubbling sounds may be heard over the hilum This of course is the optimum instant for intervention since most surely no serious damage will have taken place in the lung parenchyma

The x ray examination of the chest in which bronchial obstruction has existed more than a few hours reveals a shift of the trachea and mediastinum a narrowing of the intercostal spaces an elevation of the diaphragm on the affected side and a dense homogeneous shadow which occupies less than the normal volume of the segment or lobe involved Except when obstruction is on the basis of tuberculous bronchitis when the sputum will contain acid fast organisms laboratory studies are of little value

Postoperative bronchial obstruction is so common and so important a complication that it deserves somewhat further description This condition is indeed no more than what has previously been called postoperative pneumonia" "ether pneumonia" or some similar name which obscures the primary fact that the draining bronchi are obstructed by thick and tenacious secretion and that the patient is not able to produce an effective cough Arising most frequently following upper abdominal procedures quite regardless of the type of anesthetic agent used and after chest injury even of slight magnitude bronchial obstruction can be recognized first by an unduly rapid pulse and respiration a slight rise of temperature and by slight suppression of breath sounds usually over a lower lobe area on the side of injury or operation At this stage the roentgenogram reveals no positive findings but is merely indicative of rather poor aeration of both lung fields as a consequence of shallow respiration It is only by about the second or third day that it is possible to obtain the complete picture of atelectasis on physical or x ray examination

The proper treatment instituted at the early phase prevents progression and promptly reverts the vital signs to their proper level Withdrawal of narcotics frequent changes of posture elevation of the foot of the bed directed coughing with the chest or abdomen supported and endotracheal suction by means of catheter are nearly always sufficient to clear the bronchial tree and to reventilate partially obstructed segments It may be noted that in some instances it is necessary to continue these efforts over a period of 2 or 3 days

In more chronic cases of bronchial obstruction bronchoscopy is always indicated to determine the nature of the obstruction and—when the situation permits—to relieve it Finally if bronchoscopy does not suffice to remove the bronchial obstruction the

Much the same effect may be obtained by residence in a warm dry climate supplemented by rigorous postural drainage

ABSCESS OF THE LUNG

Although pulmonary abscess may develop as a result of some specific pneumonias in association with carcinoma of the bronchus and with many varieties of bronchial obstruction and though sometimes multiple abscesses may result from septic embolism or aspiration of stomach contents the term connotes the acute putrid variety that results from anaerobic infection The organism is the anaerobic streptococcus found especially in areas of gingivitis

Pathologically the first step in the process is a severe necrotizing pneumonia usually associated with inflammatory obstruction of the segmental or lobar bronchus involved Within a short time central liquefaction occurs and bronchial drainage begins The cavity that results however is not entirely the result of destruction but in large part derives from a valvelike action in the draining bronchus which steadily inflates the original small hiatus Definite cavitation is usually demonstrable within 5 days and fluid level in the cavity may become apparent very shortly afterward

In the preantibiotic era abscesses were classified as acute if less than 2 weeks in duration subacute if from 2 to 6 weeks in duration and chronic if older than that The practical basis of this classification lay in the fact that response to treatment varied inversely with the duration of disease The pathologic basis for this behavior is that during the first 2 weeks the process is largely exudative with very little fixed change that during the next interval fibrosis begins to fix the cavity wall and that after 6 weeks the changes are fixed and consist of dense fibrosis and bronchiectasis all about the area of original disease as well as of organization of the cavity wall with production of a permanent and unyielding defect These facts should be borne in mind since the results of antibiotic treatment of the abscess are conditioned *at least as much by its* pathologic stage at the initiation of treatment as by varying drug susceptibility of organisms

The antecedent *history* will often elicit as a predisposing cause some type of loss of consciousness so that chronic alcoholism is one of the most closely associated diseases However in a patient with impaired gag reflex or very foul mouth epilepsy head injury general anesthesia or sometimes merely extreme fatigue and very deep sleep may be the precipitating factor

The onset is usually abrupt sometimes with a chill and is manifested by rapidly rising temperature to as high as 105 F Pleuritic pain is usually marked and well localized over the affected segment Cyanosis and dyspnea are present and clubbing develops within a period of as little as two weeks Cough often severe at first is productive of only a scanty mucus but as necrosis progresses the *sputum may become dark green or dark red* with intolerable odor Sometimes when the disease follows its natural course bronchial drainage is marked by a sudden gush of a considerable quantity of malodorous pus and blood If this occurs the temperature frequently drops quickly to a subnormal level and the patient displays sweating and prostration

Physical examination of the chest in most cases reveals a lag due to pleuritic pain marked dullness which can often be established as definitely segmental in location impaired breath and voice sounds and only a few rales The favorite topographic sites for abscess are segments of the lower lobes and the axillary segments of the upper lobes although any portion of the lung may be involved The typical segments are represented by areas lying between the sixth and eighth ribs posteriorly and in the upper lobes high in the axillas

The *chest film* reveals at first a dense patch of pneumonia lying over the eighth posterior rib or just above the fissure line against the lateral chest wall Cavitation is at first slight and the wall appears thick and irregular but as the disease grows older the cavity enlarges the surrounding pneumonia is replaced by atelectasis and fibrosis and the cavity wall appears thinner Fluid level is frequent but is not necessary for roentgenologic diagnosis Lateral films will assist in the exact localization

During the acute stage of the disease there is marked elevation of the total white count with a neutrophilic leukocytosis and a left shift Sputum cultures are needed to exclude tuberculosis and fungi and to obtain drug sensitivity tests

The acute pneumonic phase of abscess has to be differentiated from ordinary pneumococcal pneumonia Poor oral hygiene a history of stupor or unconsciousness diminished breath and voice *sounds in the area of disease characteristic lo*calization within the chest and failure to respond within 24 hr to doses of penicillin adequate for pneumococcal disease are important points

Subacute and chronic abscesses must be differentiated from tuberculosis mycotic diseases and carcinoma Sputum smears and cultures and bronchoscopy are necessary measures particularly since some abscesses may have a gradual rather than dramatic onset

Treatment The treatment of all abscesses regardless of stage is at first medical In patients whose disease is treated within 2 weeks of the onset essentially complete resolution may be ex

ACUTE DIFFUSE INTERSTITIAL FIBROSIS

Described by Hamman and Rich this progressive interstitial infiltration of the lung is manifest clinically as a progressive pulmonary infection distinguished by intense dyspnea and gradually increasing hypoxia Cough is usually nonproductive Temperature ranges from 101 F upward the pulse is unduly accelerated and *cyanosis is unrelieved by oxygen* Over the chest a few medium moist rales may be heard in various areas and sometimes it is *possible to distinguish zones of consolidation* The white blood count is only moderately elevated and the film of the chest reveals nondescript pneumonic *infiltrations*

A more chronic type of diffuse interstitial fibrosis which presents extensive miliarylike infiltrations has been described under this same syndrome While in the disease as originally described death took place in from 6 to 16 weeks individuals have survived the miliary type for 2 or 3 years although hopelessly handicapped by dyspnea and hypoxia

Attempts to control this disease with ACTH and corticoids may have resulted in some amelioration of symptoms and prolongation of life Withdrawal *or reduction in dosage of these drugs may* result in rapid progression Patients who live longer than a few weeks usually present pictures of cor pulmonale and have to be treated as described (see p 1272)

LOEFFLER S SYNDROME

Transient pulmonary infiltration and eosinophilia together with few or no clinical symptoms characterize a *syndrome described in* 1929 by Loeffler Roentgenograms show unilateral or bilateral pulmonary infiltrations often fan shaped and homogeneous but these disappear in 1 or 2 weeks In Loeffler s cases the cause was unknown but similar changes have been observed in cases of cutaneous helminthiasis (*Ancylostoma braziliense*) in clonorchiasis in association with infestation with the parasites *Ascaris lumbricoides Necator americanus Strongyloides stercoralis Fasciola hepatica* and *Trichinella spiralis* in infection due to *Coccidioides immitis* in contact with the privet flower and in sulfonamide or barbiturate sensitization

Probably to be distinguished from Loeffler s syndrome is *tropical eosinophilia* a disorder which is accompanied by cough and expectoration and all the manifestations of bronchial asthma even status asthmaticus This condition has been observed particularly in natives of India and Ceylon and even among Indians living outside their country The leukocyte count is often greater than 20 000 per cubic *millimeter and the proportion of eosinophils* above 60 per cent This disorder responds promptly to arsenical therapy but relapses are not unusual

There have been few opportunities to study the pathology of these disorders In four patients with Loeffler s syndrome whose deaths were accidental the pulmonary lesions were found to consist of bronchitis bronchiolitis or pneumonia with eosinophils in the exudate and in the alveolar septums A similar disorder has been produced experimentally by the intratracheal instillation of horse serum in rabbits previously injected with the serum *Eosinophils were found in the tracheal and* bronchial mucosa congestion edema atelectasis emphysema and eosinophilic pneumonia were *found in the lungs This evidence suggests that* Loeffler s syndrome may arise from an immune reaction which takes place principally in the lungs In some of the cases of tropical eosinophilia the striking findings have been vascular and have ranged from intimal thickening of the small arteries to necrotizing arteritis with perivascular eosinophilia

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only measure to be considered is resection of the blocked segment

BRONCHOLITHIASIS

Broncholithiasis is described as a condition in which pieces of calcium of varying size roughness and irregularity are coughed out of the bronchial tree In most instances the origin of the calcium seems to be from tuberculous lymph nodes in the hilar area For unknown reasons the calcium begins to work its way out of its matrix of dense hyaline fibrous tissue and to erode into adjacent bronchi

The symptoms usually consist of repeated and rather copious hemoptyses In many instances the patient himself will report that he has coughed up fragments of gravel" Rarely is there consolidation or obstruction of the lobe from the bronchus which is being eroded Fever may occur briefly following hemoptysis and is relatively unimportant other systemic symptoms are usually absent

The diagnosis is made by the discovery either in sputum or at bronchoscopy of characteristic irregular calcium fragments The presence of dense calcification about the hilum of the lung might raise the suspicion of this condition if no other cause of hemoptysis can be demonstrated Sputum should be repeatedly searched for tubercle organisms although this effort is usually unproductive and patients with broncholithiasis on a tuberculous basis rarely if ever develop active pulmonary disease even though they may have been followed for many years

The treatment consists of reassurance once an absolute diagnosis is reached If hemoptyses are small and occur at long intervals no further measure is necessary However if hemoptyses have been large and tend to be persistent or quite frequent the only possible attack consists of the removal of the damaged bronchus and its corresponding parenchymal division Since the dissection of the hilum particularly about the pulmonary vessels is often very difficult in patients with broncholithiasis the surgeon may sometimes find himself forced either to abandon the procedure or to perform a pneumonectomy Such an outcome should be kept in mind when the problem is discussed with the patient

CHRONIC ORGANIZING PNEUMONIA
(Chronic Fibroid or Interstitial Pneumonia)

This condition in which a primary exudative reaction fails to resorb and is replaced by lymphocytic reaction and eventual fibrous change is not a primary condition but is a part of the pathologic picture in areas adjacent to chronic suppuration of the lung It is regularly present behind bronchial obstructions and in areas of incompletely resolved pneumonia as well as surrounding carcinoma abscess or bronchiectasis One of its most potent causes is bronchial obstruction The best treatment is prevention when that is possible To this end repeated bronchoscopy is often of considerable value Other measures which afford considerable benefit consist of expectorants steam inhalation and nebulized wetting agents such as Alevaire and ferments such as Tryptar Once the acute and reversible infiltration has given place to organization none of these measures has any value The patient s complaints must then be evaluated against the risks of surgical resection In many individuals resection may prove unnecessary if the patient is willing to discipline himself to the mode of life previously described under Chronic Bronchitis

CYSTIC DISEASE OF THE LUNG

Although some authorities regard all cysts as congenital in origin the consensus is that in most instances they are acquired In the newborn one occasionally encounters very large single cysts which rapidly replace an entire lung and closely simulate spontaneous pneumothorax In adults one may occasionally see single cysts which from time to time vary in size and which may eventually become infected Dyspnea due to partial compression of adjacent tissue and to the effect of the high carbon dioxide content of the poorly ventilated cyst is quite common and may be completely relieved following resection of the structure Hemoptysis may be a presenting complaint In patients without symptoms observation is sufficient but sooner or later nearly all cysts become infected or prove annoying enough to require resection

Multiple cysts of the lung are usually distributed bilaterally and give rise to a history closely resembling that of bronchiectasis On physical examination the chest is usually overdistended and presents findings characteristic of emphysema except that many moist rales may be encountered in some patients Numerous wheezes also may sometimes be heard

The x ray reveals circular shadows varying in diameter from 1 to 10 cm and scattered about both lungs In some of these there may be fluid levels but in spite of infection the walls remain quite thin Studies other than bronchography are unrevealing Iodized oil in such cases reveals irregular beaded dilatations of the smaller bronchi and bronchioles Hence the alternate name cystic bronchiolectasis Since the situation is irreparable if bilateral the treatment is palliative and does not differ from that of nonsurgical bronchiectasis

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238 NEOPLASTIC DISEASES

Champ Lyons

CARCINOMA OF THE BRONCHUS

The great majority of the neoplasms of the lung arise within the wall or epithelial lining of the bronchus either centrally or peripherally About half of all bronchogenic carcinomas are squamous cell types About one third are highly anaplastic and are designated as undifferentiated carcinoma These two types occur predominantly in males There is considerable sentiment to indict the smoking of cigarettes in the genesis of lung cancer but there are still two sides to the question More clearly carcinogenic are the industrial exposures in the mining of radioactive ores the refining of nickel the manufacture of chromates and coal gas and the processing of arsenic and asbestos The siliceous dusts as encountered in mining do not seem to increase the vulnerability of the lung to cancer

About one fifth of bronchogenic cancers are adenocarcinoma These occur with almost equal frequency in females and it has been suggested that they arise from embryonic bronchial buds They are usually highly malignant

Early lymphatic and vascular invasion are so constantly a feature of bronchogenic carcinoma that initial symptoms in many cases are attributable *to metastases These involve the mediastinal and* supraclavicular lymph nodes brain bone adrenal cortex liver and subcutaneous tissues Tumors arising in the apex of the lung may invade directly the brachial plexus and subclavian vessels producing neuritic pain Horner s syndrome and vasomotor crises in the hand and arm the *Pancoast syndrome of superior sulcus tumor* Secondary involvement of the superior mediastinum may compress the superior vena cava with resulting edema and venous suffusion of the face neck and arms the *superior vena caval syndrome* Less frequently direct invasion of the esophagus behind the heart may be responsible for obscure dysphagia

Another pattern of symptoms is to be attributed to the encroachment of the tumor upon the lumen of the bronchus or bronchiole With partial occlusion of the lumen there is persistent cough asthmatic breathing and x ray evidence of localized emphysema *As the obstruction becomes complete* there is atelectasis recurrent pneumonitis distal bronchiectasis and occasionally lung abscess Hemoptysis is fairly common in both the early and the late stages Painfully swollen joints *(pulmonary osteoarthropathy) and clubbing may* occur

Apart from the demonstration of localized emphysema and segmental atelectasis the most suggestive x ray finding is that of a hilar density extending peripherally (see Fig 167) Bronchoscopy permits visualization and biopsy of the primary tumor in 40 to 60 per cent of the cases Cytologic study of the sputum in expert hands may permit diagnosis in 85 per cent and is especially useful for peripheral tumors Early recourse to exploratory thoracotomy with biopsy of the primary tumor or regional nodes *is the procedure of choice* in any controversial diagnosis Contrast bronchography is rarely indicated

The treatment of choice for bronchogenic carcinoma is radical pneumonectomy It is of great clinical concern that about one half of the symptomatic patients presenting at an average lapse of 5 months from onset are rejected for operation on the basis of local extension or distant metastases About one third of the symptomatic cases prove to be resectable and the 5 year survival rate is about 6 per cent In older patients with reduced respiratory reserve less radical resections such as lobectomy or partial pneumonectomy with plastic reconstruction of the bronchus have proved practical without apparent reduction in the salvage rate X ray treatment and nitrogen mustard therapy occasionally retard the rate of growth and spread

Identification of the presence of a tumor before the onset of symptoms remains the chief hope for greater salvage Mass radiography for tuberculosis

has provided numerous instances of the silent and solitary nodule" Many of these have proved to be totally resectable cancers The problem of early recognition of cancer of the lung is now so pressing that all males over forty should have x ray examination of the chest at intervals of 6 months It is to be expected that refinement of cytologic techniques may contribute to early diagnosis

Carcinoma of the bronchus should also be suspected whenever any individual in the susceptible age group shows delayed resolution of any intrapulmonary inflammation The unresolved pneumonia or a lung abscess or pneumonia recurrent in the same lobe in males over forty should invite immediate study for tumor

BRONCHIOLAR CARCINOMA

This disease has been known as *pulmonary adenomatosis* but the ultimately fatal outcome and the increasing recognition of regional and distant metastases render suspect the identity of completely benign pulmonary adenomatosis It is not certain whether the tumor cells are derived from the basal cells of the terminal bronchioles or from the lining membrane of the alveoli Usage dictates preference for *alveolar cell carcinoma* or *bronchiolar carcinoma* There occurs in sheep a contagious disease of presumptive viral etiology known as *jaag iekte* in South Africa and as *Montana chronic progressive pneumonia* in the United States This disease is not transmissible to man but is characterized by hyperplasia of cuboidal epithelial cells within the alveoli in striking similarity to the neoplastic disease of man

The tumor appears to arise from multicentric foci and ultimately involves both lungs Both sexes are susceptible and the usual age of onset is in the fourth and fifth decades Symptoms begin insidiously often following an acute respiratory infection Cytologic examination of the sputum even in early cases frequently reveals tumor cells Dyspnea because of faulty gas exchange is out of proportion to x ray findings Cough productive of the typically viscid pinkish sputum is a manifestation of the tumor Terminally there is frank hemoptysis with clubbing intense cyanosis recurrent pneumonitis and evidence of metastasis Nodular and confluent patterns of the disease are recognized

The treatment of choice is surgical excision of the initially involved lobe or lobes when practical There is some hope of palliation by x ray therapy but nitrogen mustard appears useless

ADENOMA OF THE BRONCHUS

The bronchial adenoma is a locally invasive and occasionally metastasizing tumor derived from the



Fig 167 Carcinoma of the bronchus

mucous glands of the bronchus and requiring separate classification from the more rapidly growing bronchogenic carcinomas It constitutes about 3 per cent of all lung tumors and differs from bronchogenic carcinoma in that it is usually apparent before the fifth decade lacks sexual predilection and develops metastases persisting for long periods without apparent change

Histologically the adenomas show a peculiar epithelial proliferation and an equally peculiar stroma Inclusions of bone are thought to represent metaplasia from chronic infection The mixed tumor (cylindroma) type (10 per cent) is somewhat more invasive than the carcinoid adenoma (90 per cent) There is still controversy about these tumors as regards etiology the occurrence of mixed types the absence of argentaffin granules in the types designated is carcinoid and their relationship to other polypoid tumors of the bronchial wall

The adenoma syndrome is the clinical consequence of the slow growth of a vascular tumor producing major bronchial occlusion in a young person i e hemoptysis asthmatic wheezes obstructive emphysema recurrent pneumonitis and the complications therefrom bleeding atelectasis bronchiectasis pleuritis lung abscess and empyema The lower lobes are more often affected and there is a slightly greater incidence on the right side Contrast radiography (bronchography or tomography) often demonstrates the tumor but routine x rays are noncontributory in about one fifth of the cases About 90 per cent of the tumors may be recognized bronchoscopically by their polypoid appearance mobility vascularity and absence of

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appear after removal of the tumor The diffuse mesotheliomas require difficult differentiation from metastatic anaplastic carcinoma with pleural effusion and are characterized by a comparably intractable course Treatment is limited to repeated thoracenteses radiation therapy and instillation of radioactive gold as palliative procedures

The Solitary Pulmonary Nodule Occasionally a roentgenogram of the chest may reveal a nodule less than 6 cm in diameter which is fairly sharply delineated from adjacent pulmonary tissue Such lesions have been designated *solitary pulmonary nodules* in preference to the term *coin lesions* About one third of these are peripheral bronchogenic carcinomas demonstrable as such only after excision and surviving in 75 per cent of the patients when treated usually by simple lobectomy In the absence of other diagnostic aids thoracotomy is indicated by the x ray findings in most cases Ten per cent of such lesions are metastatic neoplasms and about half are granulomas with histoplasma tuberculosis and coccidioidomycosis responsible in that order Hamartomas lipid granulomas lipid granulomas from oily nose drops and pulmonary sequestrations also produce this picture A non operative program of continued observation may be elected when a review of earlier films demonstrates no change over a period of 5 years but it should be realized that such nodules have been followed for 8 years only to declare themselves as cancers Considerable interest in radiologically demonstrable calcium deposits has demonstrated that flecks" of calcium may occur in bronchogenic cancers A central core or concentric lamellations of calcium are indicative of granuloma

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239 DISORDERS DUE TO ASPIRATED FOREIGN BODIES

John S Chapman

The aspiration of large foreign bodies which is encountered most commonly in children is marked by the sudden onset of strangling choking coughing and cyanosis If the object is small enough to pass down to a lobar or branch bronchus the acute picture subsides for a few days and then the syndrome presented is that of bronchial obstruction with suppuration beyond particularly when the offending substance is vegetable In other cases if the body is nonabsorbable after coming to rest in one branch bronchus with a subsidence of symptoms it may after a few days become dislodged and again repeat the original episode as it is shuttled about in the trachea and major bronchi There is only one treatment—bronchoscopy with removal

Lipid Pneumonia This condition results from the aspiration of oily material and occurs most commonly in patients who have ingested large quantities of mineral oil over a prolonged period or in infants or adults who have been subjected to the use of oily nose drops In a limited area and to a minor extent a lipid pneumonia probably takes place following every injection of iodized oil The histologic picture is that of foreign body giant cell reaction with lymphocytes and mononuclear leukocytes In chest films one usually finds a bilateral lower lobe distribution which is patchy and irregular but occasionally the infiltration may be found involving other areas and even single segments The earliest phase is said to be indicated only by increased basilar markings The sputum examined fresh under the cover glass reveals numerous free fat droplets as well as phagocytes filled with oil droplets which take up Sudan III

No treatment is indicated for lipid pneumonia and the condition is of importance chiefly from the fact that a problem of differential diagnosis arises as a result of routine film of the chest Obviously a cessation of the use of oil is necessary to prevent the development of additional areas of infiltration

Aspirational (Enzymatic) Pneumonia This type of pneumonia is the result of the aspiration of gastric contents Usually a period of unconsciousness associated with vomiting as in acute alcoholism suicidal efforts head injury or rough anesthesia is a major predisposing factor Occasionally similar types of illness follow tracheoesophageal fistulas as a result of carcinoma in adults or as a congenital anomaly in infants The so called esophageal spill over syndrome associated with esoph



FIG 168 Hematogenous metastasis from sarcoma of the ileum clinically marked by intense dyspnea and cyanosis (*Courtesy Dr C L Martin*)

ulcerations The vascularity dictates caution in the indicated biopsy The lack of ulceration explains the absence of tumor cells in sputum and bronchial washings

Older methods of piecemeal excision by repeated bronchoscopic nibblings have largely been replaced by direct surgical removal of the primary tumor the involved hilar lymph nodes and the secondarily diseased lung Exceptions to pneumonectomy consist of lobectomy for the more peripheral tumor without involvement of hilar nodes and bronchotomy for the small tumor with a tiny stalk Long term survival is the rule especially for the carcinoid adenomas Mediastinal recurrence and hepatic metastases are an especial hazard of the mixed tumor adenomas (cylindromas) There is some evidence to suggest that true bronchogenic carcinoma may occasionally develop within an adenoma

METASTATIC TUMORS OF THE LUNG

Metastasis to the lung results from infarction with tumor emboli carried by the peripheral veins The x ray appearance is frequently characteristic and may appear as a solitary cannonball nodule multiple nodules (see Fig 168) or miliary dissemination known as *lymphangitic carcinomatosis* (see Fig 169) It is hazardous to make an x ray diagnosis of lymphangitic carcinomatosis of the lung in the absence of clinical evidence of alveolar capillary block namely severe dyspnea and obvious cyanosis Sarcomas hypernephromas melanomas and tumors of the testicle breast thyroid and pancreas seem to find the lung an especially favorable site for the growth of metastases

Dyspnea and pleuritic pain are the cardinal symptoms of lung metastases Erosion into the bronchial tree may be associated with cough hemoptysis and occasionally with tumor cells in the sputum Treatment is largely palliative with opiates and repeated thoracenteses to relieve the pain and dyspnea Irradiation may prove helpful for sensitive tumors but more reliance is placed upon hormonal or isotope approaches for specific tumors

In the course of exploratory thoracotomy for asymptomatic solitary nodules it occasionally happens that a metastasis from a previously unidentified primary tumor is found The ground rules for deliberate surgical excision of solitary lung metastases include prior control of the primary focus lapse of a reasonable length of time between initial treatment and appearance of the lung metastasis and absence of other areas of tumor recurrence

Primary Tumors of the Pleura Localized pleural tumors are usually proved to be mesenchymomas of subpleural mesodermal elements or granulomatous inclusion cysts complicating interlobular inflammation Primary pleural neoplasms are restricted to the mesothelioma This may occur as a localized tumor frequently arising from the visceral pleura or embedded in the lung and distinctively associated with clubbing and arthralgia which dis



FIG 169 So called "lymphangitic carcinomatosis" metastatic from a carcinoma of the cervix (*Courtesy Dr C L Martin*)

respiratory tract whereas others affect chiefly the deeper structures of the lung, is partly attributable to their varying solubility in water Ammonia formaldehyde hydrofluoric and hydrochloric acid are so soluble as to attack the first moist surface with which contact is made The concentration of these chemicals in the air going to the deep parts of the lung is thus reduced to some extent on the way through the upper passages and pulmonary injury is lessened In contrast nitrogen dioxide (nitrous fume) phosgene and cadmium oxide fumes are relatively less soluble and hence less irritating to the upper respiratory tract They can be respired without great discomfort and reach the deeper parts of the lung in atmospheric concentration that may be exceedingly injurious The reaction to these chemicals is delayed but often far more serious than that to those causing more immediate discomfort In fact the lack of distress immediately upon inhalation makes these gases especially dangerous Midway between these two groups in solubility and action are sulfur dioxide the halogens and hydrogen sulfide

Treatment of the acute reaction depends little or not at all upon the recognition of the specific noxious agent responsible for the event Therapy is directed first at overcoming the alterations of physiology Shock must oftentimes be combated Oxygen in concentrations of 50 per cent or more is imperative There is little scientific support for the use of positive pressure by mask although a priori reasoning has prompted its use Practical experience has shown that physical struggle and unrest may cause sudden death If positive pressure during inspiration makes breathing less of an effort and is tolerated without restlessness it is not contraindicated except in shock In the hypotensive state due to poor venous return positive pressure breathing is contraindicated The use of agents which lower the surface tension of serum might be useful when administered via the airway as recommended in pulmonary edema of circulatory origin but the author has no information on this point Sedation is very important Bromides appear to be preferable to barbiturates Morphine is contraindicated The prophylactic use of antibacterials is recommended throughout the period of pulmonary inflammation

Other relatively acute reactions of the lung to inhaled material are noteworthy because of the long delay between initial contact and the reaction Although exposure to high concentrations of a fume thought to be anhydrous beryllium sulfate may cause a violent chemical pneumonitis in a few to 72 hr a much more insidious chemical pneumonia (not to be confused with the chronic granuloma discussed later) is also known to occur in the beryllium extraction industry and in other exposures where beryllium fluoride and beryllium oxide are inhaled In this reaction which develops weeks or even months after exposure begins the symptoms of dyspnea on exertion paroxysmal cough substernal pain weakness and weight loss may precede the development of any abnormal shadows seen in the roentgenogram of the chest by 1 to 3 weeks When abnormal shadows develop they are characterized by a granular haziness of a diffuse patchy distribution which in some instances may be fluffy in appearance The pathology is that of a true chemical pneumonia Treatment is the same as for the acute reactions described before This disease is apt to persist for several weeks and treatment must be continued throughout The use of ACTH or cortisone has not received adequate trial but should be explored Recovery is the rule but fatalities do occur

A rather rare disease brought about by the inhalation of bagasse dust has been described in workers preparing bagasse from sugar cane or using it in manufacture The true etiologic factor is unknown but its association with bagasse seems established and for the present the disease might be properly included under the heading of this chapter Weeks to months after the beginning of exposure to bagasse dust the disease makes its presence known by severe paroxysmal cough and dyspnea Fever may persist for weeks or months The lung shows evidence of resistance to expansion Cyanosis may be present The white blood count is elevated the polymorphonuclear cells forming 70 to 90 per cent of the total The clinical picture is that of a diffuse pneumonia which persists for weeks The scant tissue available for study shows an interstitial fibroelastic reaction The pulmonary roentgenogram shows an abnormal diffuse pattern of fine stippling Recovery is slow but usually occurs and few if any sequelae remain Treatment is symptomatic The use of ACTH or cortisone has not been reported

Chronic Reactions As mentioned earlier the majority of the various kinds of material inhaled and deposited in the lung cause no tissue reaction Particles larger than 10 μ in size are not found in the deeper parts of the lung but those of smaller size do reach the alveoli where they are engulfed by phagocytes Soluble particles such as marble or gypsum disappear entirely while those less soluble or insoluble particles are carried by the phagocytes to the lymphoid collection of the lung and mediastinum and there deposited Many of the insoluble varieties of dust are inert so far as tissue reaction is concerned and do not cause significant fibrosis The particles of such substances as iron soot etc simply remain in the lymphoid tissue along the course of the lymphatic and blood vessels that accompany the bronchial tree If present in large enough quantities these inert substances may

ageal stricture or obstruction without fistula produces a somewhat similar type of pulmonary disease

Both lower lobes usually reveal a very intense bronchopneumonic infiltration Acute necrosis leads to the formation of abscesses toward the termination of smaller bronchi These abscesses are notable for the absence of fibrous tissue reaction and for the fact that their walls consist principally of a slimy membrane beyond which is a zone of intense necrosis The peculiarities of this reaction are thought to be the result of the action of gastric ferments on pulmonary tissue The tissue reaction resembles that of abscesses due to the aspiration of vegetable foreign material

The clinical picture is that of an acutely ill patient with marked dyspnea and cyanosis The lower lobe areas present moderate reduction in breath sounds and fairly numerous moist rhonchi and rales Polymorphonuclear leukocytosis is marked The sputum may contain identifiable gastric contents and it may be possible to demonstrate peptic activity in expectorated material Roentgenograms reveal patchy infiltrations bilaterally but it is often impossible to distinguish individual abscesses

The treatment for all these conditions is repeated bronchoscopic aspiration the use of large doses of penicillin and in the fistula cases efforts to correct the condition In the case of the adult whose carcinoma of the esophagus (see Chap 243) has invaded the bronchus or trachea there is of course the possibility of gastrostomy as a partially palliative measure The outlook in such instances is so bad and the usual duration of life so short after perforation that there is little chance for intervention and even less that the intervention will be successful

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240 PULMONARY DISORDERS DUE TO INHALATION OF NOXIOUS AGENTS

George W Wright

General Considerations For centuries it has been recognized that certain particulate substances cause no untoward effects even when inhaled for many years whereas others may rapidly or gradually cause pulmonary changes that vary considerably in degree of severity and seriousness The number of known pathogenic substances continues to increase with the recognition of previously obscured relationships and with the development of new substances or new situations to which men may be exposed

The body response to these noxious agents is of two broad categories acute pneumonitis and chronic granuloma with fibrosis The acute response may be immediate or delayed hours or even days after the contact in the chronic form there is with one exception a history of prolonged exposure and a delay in development of the body reaction Because of the trend toward a delayed reaction the inciting cause may be difficult to discover except by the most painstaking anamnesis In no other category of disease is the past history more important and at the same time apt to be so poorly explored Most physicians have little contact with and knowledge of specific working conditions in industry and hence they are likely to be ill prepared to take an occupational history No occupational history is adequate until the activities and surroundings of the patient during every year of his life are accounted for and the potential for hazard of each specific occupation is known

Acute Reactions The acute pulmonary injuries usually arise from the inhalation of irritant vesicatory or necrotizing gases or fumes Certain gases have an immediate powerful irritating action which is characterized by lachrymation burning and pain of the nose pharynx and trachea and by severe cough Strong concentrations may cause such severe irritation as to bring about prompt cessation of respiration allegedly by laryngeal spasm If the subject survives the immediate effects of the gas pulmonary edema may ensue with subsequent recovery or death in spite of all efforts to provide relief Other gases for example the nitrous fumes of detonated blasting powder or burning celluloid may not cause such severe immediate reactions as to be unduly alarming but after a delay of several hours the patient may rather rapidly develop severe respiratory distress cyanosis and shock with all the signs of pulmonary edema and exudate Because serious delayed reaction is possible it is wise to keep all persons who have been exposed to unusual concentrations of the irritating gases under close scrutiny for at least 24 hours Some degree of inflammation and necrosis of tissue always occurs following severe pulmonary reactions and during this period the lungs are unusually susceptible to bacterial infection Recovery may occur by resolution of the edema and inflammatory products or by fibrous replacement Commonly there are no recognizable residua or sequelae

That certain gases act primarily on the upper

respiratory tract whereas others affect chiefly the deeper structures of the lung is partly attributable to their varying solubility in water Ammonia formaldehyde hydrofluoric and hydrochloric acid are so soluble as to attack the first moist surface with which contact is made The concentration of these chemicals in the air going to the deep parts of the lung is thus reduced to some extent on the way through the upper passages, and pulmonary injury is lessened In contrast nitrogen dioxide (nitrous fume) phosgene and cadmium oxide fumes are relatively less soluble and hence less irritating to the upper respiratory tract. They can be respired without great discomfort and reach the deeper parts of the lung in atmospheric concentration that may be exceedingly injurious The reaction to these chemicals is delayed but often far more serious than that to those causing more immediate discomfort In fact the lack of distress immediately upon inhalation makes these gases especially dangerous Midway between these two groups in solubility and action are sulfur dioxide the halogens and hydrogen sulfide

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stimulate sufficient proliferation of fibrous tissue along the lymphatic channels to cause the shadows cast by normal pulmonary vascular markings to be exaggerated as to size density and projection toward the periphery Indeed if the inert material is dense enough—as is iron for example—the concentrated metallic deposits may themselves cause a shadow easily seen in the roentgenogram Although *these inert substances do cause a slight proliferation* of fibrous tissue in their immediate vicinity the reaction is mild and there do not appear to be any recognizable evidences of interference with either the physiologic or immunologic functions of the respiratory apparatus from their retention In contrast to these so called "inert" particulate substances there are others which when inhaled cause definite tissue reaction

PNEUMOCONIOSIS

Pneumoconiosis is a generic term embracing all chronic changes in the lung induced by the prolonged inhalation of dust of a nonliving character with no implication as to the type or severity of the change This definition is so broad that the term *no longer connotes disease The necessity for some* such term is obvious when one realizes that only a few of the inhalable substances truly cause a pulmonary change that results in sufficient dysfunction to warrant the appellation of disease The pneumoconioses of importance to health are silicosis asbestosis coal workers pneumoconiosis (South Wales) pulmonary granulomatosis of beryllium workers Shavers disease and diatomaceous earth pneumoconiosis Of these silicosis asbestosis and coal workers pneumoconiosis (South Wales) have broad socioeconomic implications in addition

Siderosis Siderosis one of the pneumoconioses generally termed benign because it has no demonstrable significance as regards health nevertheless has definite economic implications because its pulmonary radiographic appearance mimics simple silicosis Since it may occur in conjunction with industries which also are known to produce silicosis the differential diagnosis is of considerable importance A detailed history indicating heavy exposure to inhalation of iron oxide rather than free crystalline silica will usually establish the diagnosis When pulmonary nodulation develops in a person who has done welding oxyacetylene cutting of iron or mining of hematite in atmospheres heavily contaminated with crystalline silica particles the differential diagnosis may require lung biopsy

Silicosis Silicosis is a disease of the lungs caused by the prolonged inhalation of fine particles (less than 5 μ) of free crystalline silica (SiO_2) in quantities sufficient to produce the characteristic fibrosis It is manifested clinically by the development of discrete nodules confined to the lung and lymph nodes of the mediastinum *by an increased susceptibility* to tuberculosis and by a paucity of symptoms and signs during the discrete nodular phase of the disease Severe evidences of respiratory embarrassment are likely to develop when conglomerate masses and secondary emphysema develop in the lungs

With the exception of asbestos the various silicates and amorphous silicas produce little or no reaction in the lungs Silicosis therefore is associated only with those pursuits that expose one to the inhalation of naturally occurring or artificially produced forms of free crystalline silica The common form of free silica is quartz which is abundantly distributed in the earth s surface Mining tunneling rock cutting sandblasting abrasive manufacture and use ceramic manufacture foundry work and glass manufacture are among those industries associated in certain jobs with the production or handling of finely divided free crystalline silica Not all jobs or locations in these industries expose the worker to hazardous quantities of silica For example coremakers in most foundries have little exposure to silica whereas the sand *reconditioner or shake out operator may have* considerable If however the coremaker works in a common room he may be exposed to an adjacent silica hazard One can readily understand that an occupational history disclosing only that the occupation was miner or foundryman is entirely inadequate Intimate knowledge of the job working place duration of various jobs and even the actual place in which the work is done is an absolute necessity Anything less is inadequate data on which to evaluate the exposure of a given individual

The silica particles that enter the alveoli and respiratory bronchioles are 10 μ or under Most visible dusts are made up of particles larger than this It has also been shown that silica particles between 5 and 10 μ act only as a foreign body and that the active or fibrogenic component of hazardous silica dust is from 1 to 5 μ Many extremely dusty atmospheres as tested visually are really quite harmless so far as the lung is concerned The reverse may be equally true some very harmful exposures being where there is little visible dust The occupational history must therefore elicit information about particle size as well as about the chemical nature of the dust

It has been amply demonstrated that the total number of particles of hazardous size inhaled is an important consideration in determining the severity of pulmonary injury Contrary to popular belief the black native labor of the South African gold fields has a relatively low incidence of silicosis This is thought to be attributable to the fact that the individual usually works *only 9 to 18* months

underground The whites working in the same areas have a much higher incidence because they are employed on a long term basis

It is obvious from these considerations that the size and concentrations of hazardous particles and the duration of exposure are important determinants of whether or not silicosis will develop in a given individual There is also a factor of individual variation that is related to the effectiveness of the individual's "air filter" and lung cleansing mechanism There is acceptable experimental and clinical evidence to show that when the reticuloendothelial system of the lung is saturated with inert foreign material less than the usual amounts of silica will produce silicosis This has an obvious practical implication

Experience has shown that dusts containing fewer than 5 million particles of free silica 10 μ or less in size per cubic foot will rarely cause silicosis in the normal working span of a man Concentrations above 100 million are considered very unsafe for more than a few months of exposure Under most working conditions of the past it took 10 to 20 years of exposure to produce recognizable silicosis Exceptional circumstances have been reported where unusual exposures of 2 or 3 years duration produced the disease Men exposed approximately a year to high concentrations of virtually pure silica develop a nonnodular change having more the appearance of a chemical pneumonia

In most occupations the inhaled dusts are a mixture of silica and other substances There is no doubt that these accompanying dusts as for example gypsum or iron are capable of modifying the activity of the silica in such a way as to diminish and delay its fibrogenic action In the experimental animal finely divided aluminum hydrate and metallic aluminum have both been shown capable of so modifying the action of silica as to prevent the development of significant fibrosis

After the silica particles reach the alveoli they are picked up by phagocytes These migratory cells carry their engulfed particles to regional lymphoid clusters and to the large nodes of the hilum and mediastinum The actual process whereby the silica particles stimulate cell proliferation and fibrosis is unknown but appears to be a physicochemical process associated with surface phenomena In the areas where the particles accumulate fibroblastic proliferation and hyaline formation produce nodules of a characteristic whorled appearance At first these silicotic nodules are found only in the larger lymph nodes but as lymph drainage becomes progressively more impaired the particles accumulate in the peripheral lymph channels along the course of the blood vessels especially those of the pulmonary artery The tissue reaction in these areas gives the vessels a beaded appearance which can be recognized in a pulmonary roentgenogram but not differentiated from the beading caused by dusts which are entirely free of silica As more and more silica is accumulated in the periphery of the lung the tissue reaction increases to form nodules which alone or by merging with other nodules achieve a size and density sufficient to cast a shadow on the roentgenogram Reconstruction of the nodules in man has demonstrated that they usually form around compress and finally close off a blood vessel of the pulmonary artery tree Around each nodule there is a zone of dilated air spaces described as focal emphysema At this stage the nodules are discrete and comprise a relatively small amount of the total lung tissue The lung between the nodules has a normal appearance This stage of silicosis has been categorized as simple discrete nodular silicosis Some subdivide this group on the basis of the size of the nodules seen in the roentgenogram

In many individuals the reaction does not progress beyond the discrete nodular stage In others large irregular masses of very dense fibrous tissue with irregular radiating strands develop As a rule this occurs in the upper parts of both lungs In advanced stages the entire upper part of both lungs may be a dense shrunken mass of fibrous tissue firmly adherent to the chest wall with the lower parts of the lung the site of severe diffuse emphysema In some instances it appears that these masses form by a shrinking together of the lung and conglomeration of the nodules In others there is little shrinkage but rather an extraordinary proliferation of fibrous tissue When massive or conglomerate shadows appear in the roentgenogram the disease is categorized as complicated or *conglomerate silicosis* Rarely the conglomerate form appears with little or no discoverable accompanying discrete nodulation

Histologic study reveals that in 60 to 70 per cent of those persons exhibiting the conglomerate form of silicosis evidences of tuberculosis can be found associated with the pulmonary masses In the remainder nontuberculous infection may have played a role in causing the intense proliferation of fibrous tissue It seems logical to believe that previous nontuberculous infection may so damage the self cleansing mechanism of the lung that unusual amounts of silica are likely to be retained at the site of previous infections and thus cause unusual fibrotic response in these areas

The diagnosis of silicosis requires that one see nodulation characteristically distributed throughout the lungs in the roentgenogram that other causes of the nodular pattern be ruled out and that a history of exposure to the inhalation of free crystalline silica of particle size and amount capable of causing the nodular fibrosis be obtained These requirements may seem unduly strict in view of the

fact that a histologic stage of the disease must precede the clinical manifestations. The tendency to make a diagnosis of silicosis solely on the basis of a history of exposure to silica is certainly not realistic because in actual practice the majority of persons so exposed never develop clinically significant evidences of the disease. To make the diagnosis on the basis of a positive occupational history and the presence or development of exaggerated bronchovascular shadows will lead to frequent false diagnoses. Many persons who have inhaled nonsilica dust and some with no history of any dust exposure at all will be found to have markedly exaggerated bronchovascular markings. To require nodulation demonstrable by roentgenogram in order to establish a diagnosis is justifiable both from a medicolegal point of view and from that of the person's health since no clinical significance is attached to the prenodular stage of silicosis.

In the simple discrete nodular stage of silicosis there are few related symptoms. Numerous investigators studying silicotic persons from several industries have found only slight evidences of impaired cardiorespiratory function. Many silicotics show entirely normal measurements during this stage. In others there is a moderate reduction of maximal breathing capacity and an absolute increase of residual air. These findings are evidence of slight diffuse obstructive emphysema. When conglomerate masses develop these evidences of emphysema are likely to become more severe and may lead to complete respiratory crippling. In the simple discrete nodular stage there is no impairment of gas diffusion between the atmosphere and pulmonary blood. In the conglomerate stage poor mixing and distribution associated with emphysema lead to a lowered alveolar pO_2 and some degree of arterial hypoxia may develop during exercise. The physiologic abnormalities of conglomerate silicosis are caused primarily by the diffuse obstructive emphysema which accompanies this stage of silicosis. The complaint of exertional dyspnea is due almost entirely to a reduction in the ability to pump air into and out of the lungs. At this stage the clinical symptoms in addition to dyspnea on exertion are cough, expectoration, chest pain and weakness. Cor pulmonale is a late complication and is the cause of death in many instances.

Discrete nodular silicosis appears to be progressive for a year or two after the individual is removed from exposure but then stabilizes and life expectancy appears normal. The conglomerate form progresses slowly even after removal from exposure and life expectancy is diminished.

Tuberculosis is the most feared complication of silicosis. Some individuals having simple discrete nodular silicosis may develop active tuberculosis, the characteristic infiltrates or cavities going through the conventional pattern that eventuates in subsequent spontaneous healing. This combination is best referred to as silicosis *with* tuberculosis and is reported to respond favorably to antibacterial therapy for tuberculosis. More often than not, however, active tuberculosis is prone to pursue one of three courses in the person with silicosis. In the unusual circumstance of a primary or hematogenous infection occurring in lungs already the site of silicosis one finds that the peripheral zone of the silicotic nodule is a preferred site for the development of the tuberculous lesion. Previously sharp borders of the shadow of the nodule in a roentgenogram become blurred and the nodule enlarges. The tuberculous process proceeds with enhanced speed and practically always ends fatally. Reactivation of a preexisting tuberculous focus or the occurrence of exogenous reinfection may lead to rapidly developing cavitation. The disease may then become widely disseminated and will run a rampant and fatal course. In these two types of reaction the tuberculosis is the most prominent feature. Spontaneous recovery is so unusual and the clinical course so adverse that this modification of tuberculosis warrants the designation of silicotuberculosis.

A third combination occurs when silicosis and tuberculosis exist together in such a way as to produce massive fibrosis. The presence of conglomerate shadows in the silicotic person is assumed on statistical grounds to indicate complicating tuberculosis although tuberculosis can be proved in only about 70 per cent of the cases. The silicosis and tuberculosis both are modified to the extent that they produce massive fibrotic conglomerates in which silicotic nodules and the granuloma of tuberculosis can be recognized histologically. Clinically the tuberculosis is modified by becoming very indolent and losing all or most of its invasive and disseminating character. This combination is termed tuberculosilicosis and can exist for many years with few if any symptoms other than cough and dyspnea on exertion.

Anthracosilicosis is a variant caused by the inhalation of a mixture of coal dust and free crystalline silica. In essence its course is very similar to conventional silicosis. It appears that emphysema may develop earlier and be more of a complication in the simple discrete nodular phase in anthracosilicosis.

The type of pathologic process which characterizes silicosis affords little hope of any form of effective treatment for the patient having well established disease. Prevention by adequate control of all dust hazards is the answer to the problem. Aluminum powder has definite prophylactic action in animals and presumably would also be effective in humans unavoidably exposed to silica. No critical

data on this point are available Aluminum by inhalation has been recommended and tried as an agent to relieve the symptoms of silicosis Critical data fail to support its effectiveness except as a form of psychotherapy When active tuberculosis is a complication antimicrobial therapy may be effective in the discrete nodular stage but has little if any influence on the massive conglomerate stage Experience suggests that in the simple discrete nodular stage continued employment is well tolerated It has been argued that in the conglomerate stage physical work is deleterious No critical evidence bears on this important point The silicotic man should of course be protected from any additional silica hazard in the environment

Coal Workers Pneumoconiosis Exposure to the inhalation of coal dust without substantial quantities of silica appears to be rare at least in the United States Because of this and the fact that pure coal dust or carbon inhalation by animals produced no reaction similar to silicosis it has been accepted that the nodulation and conglomerate masses seen in coal miners is in reality a modified form of silicosis Recently the Pneumoconiosis Research Unit of Cardiff South Wales has reported studies strongly suggesting that in the miners of that area pulmonary injury occurs from the inhalation of coal per se rather than from the inhalation of silica Histologic studies show that the earliest change is the deposition of pigment in a stellate shaped discrete macule about which is a zone of emphysema There is a delicate network of reticular fibers in these pigmented areas but characteristically there is no hyaline deposition or extensive fibrosis such as typifies the silicotic nodule These macules with their zone of focal emphysema are numerous and scattered throughout both lungs This stage of the disease is categorized as simple pneumoconiosis of coal workers and is recognized in the roentgenogram by tiny nodulations which may coalesce into larger nodules or mottlings The disease remains at this stage if no further exposure occurs and is characterized by a lack of symptoms Physiologic studies show little or no abnormality of function in spite of the focal emphysema When as happens occasionally a person with evidence of severe emphysema is seen at this stage a nonindustrial or spontaneous origin of the emphysema must be strongly considered

In certain cases of simple pneumoconiosis irregular large localized masses appear and progress in size This stage is termed *progressive massive fibrosis* or *complicated pneumoconiosis* of coal workers This stage is thought to be caused by coexistent infection and tuberculosis is implicated in a high proportion of the cases As the massive fibrosis develops severe obstructive emphysema usually but not always becomes apparent

It is of interest that this entity so closely parallels conventional silicosis differing chiefly in that the focal emphysema is said to be more severe and the degree of fibrosis much less severe in the simple uncomplicated stage of coal workers pneumoconiosis than is true of silicosis Also a high incidence of active tuberculosis and its rapid progression have not been reported in coal workers pneumoconiosis Typical changes have been reported in coal trimmers where silica exposure is considered nonexistent hence the conclusion that they are the result solely of coal dust There is a divergence of incidence in different geographic locations of South Wales and the incidence for South Wales is much higher than in other coal fields of Great Britain

There are no critical studies to demonstrate whether or not this entity exists in other coal mining areas Similar cases both radiographically and histologically are alleged to have been demonstrated in the United States Many questions remain to be studied before the proper meaning of this interesting study from South Wales can be assessed in terms of the coal workers of other areas

Asbestosis The prolonged inhalation of sufficient quantities of asbestos fiber produces a diffuse fibrosis of the lung which may be extremely severe The disease offers a contrast to silicosis in many features Long fibers (20 to 50 μ) rather than short fibers evoke the tissue response the irritant is mechanical rather than chemical the lymphatic system is involved only slightly and late the early lesion being a peribronchial fibrosis the fibrosis is diffuse rather than nodular in character severe pleural changes are common interference with the passage of oxygen from the alveolus to the blood because of thickened alveolar walls is the characteristic physiologic alteration diffuse obstructive emphysema is not manifested clinically or physiologically clinical symptoms and physiologic abnormalities may precede unequivocal roentgenographic evidences of asbestosis there is no alteration of susceptibility to tuberculosis The diseases are similar in that the quantity of proper sized particulates inhaled is the chief determinant of the development of diseases Under usual working conditions years of exposure are required to produce the disease Severe disability (entirely different in fundamental character from that of silicosis) is likely to be present only in advanced cases cor pulmonale though a common cause of death in both is more frequent in asbestosis There is no effective form of treatment for the disease per se

Pulmonary Granulomatosis of Beryllium Workers An unusual chronic granuloma of the lung has been described in persons working where they may be exposed to the inhalation of beryllium and its compounds Although an association with industries using beryllium compounds has been proved the

etiologic factors have not been determined The disease is characterized in the severe form by extreme exertional dyspnea paroxysmal cough marked loss of weight and cyanosis the roentgenogram shows a diffuse ground glass appearance of the lungs plus enlargement of the hilar lymph nodes Interference with diffusion of oxygen across the alveolar membrane is the underlying physiologic defect and cor pulmonale the usual cause of death Minute exposures to the chemical and delay of months to years between exposure and onset of the disease make this a most bizarre entity The disease has more than just industrial implications since bona fide cases have developed following the inhalation of exceedingly minute quantities of beryllium under nonindustrial circumstances The number of cases is increasing Differential diagnosis from other nodular granulomas is at times most difficult No authentic spontaneous complete recovery has been reported The mortality rate is high but many persons remain in an arrested state of the disease for years ACTH and cortisone have produced dramatic but not permanent remissions

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Section 5 The Alimentary Tract

241 DIAGNOSTIC CONSIDERATIONS

Thomas E. Machella

The more important manifestations of disorders of the alimentary tract have already been discussed. They include dysphagia (p. 127), indigestion (p. 118), constipation (p. 132), diarrhea (p. 132), and ileus (p. 45). The section to follow will deal with the alimentary disorders from the standpoint of specific diseases rather than symptoms. Before discussing these specific diseases, certain general principles will be considered.

FUNCTIONAL DISORDERS OF THE GASTROINTESTINAL TRACT

No attempt will be made to discuss functional disorders of the gastrointestinal tract in detail. It must be pointed out, however, that such disorders, especially of the motor functions, exist and that they are very frequently responsible for gastrointestinal complaints. Functional motor disturbances which may be associated with definite symptoms include esophagospasm, cardiospasm, gastric hypo- and hypermotility, spasm of the pylorus, spasm of the gastric antrum, spasm of the first and second portions of the duodenum, very rapid or delayed gastric emptying, duodenal stasis, small intestinal hyper- or hypomotility, and various spastic and atonic states of the colon. Secretory disturbances of significance are those of excessive secretion of highly acid juice by the stomach and of mucus by the colon. Though a temporary functional gastrointestinal disturbance may occur in a healthy person under the influence of an emotional upheaval, more prolonged and severe changes in gastrointestinal functions on an emotional basis may lead to actual morphologic changes in the gastrointestinal tract, depending not only on the nature, intensity, and duration of the emotional stimuli but also on the relative influences of the two effector divisions of the autonomous nervous system and the susceptibility of various portions of the gastrointestinal tract. Examples of actual organic changes on the basis of emotional disturbances, in the opinion of this writer, include peptic ulcer, chronic gastritis, duodenitis, ulcerative colitis, regional enteritis, and megaesophagus on the basis of cardiospasm. These diseases occur in those who are high strung and hypersusceptible reactors to stimuli when they are subjected to a variety of emotional frustrations and insults. The successful medical management of such patients calls for a sincere, understanding, helpful, and sympathetic attitude on the part of the physician, combined with an ability to instill confidence and hope. Induction of remissions and reduction in the incidence of relapses depend on the discovery and successful solution of the emotional problems responsible. Usually a good doctor can handle such problems satisfactorily, but occasionally expert psychiatric aid may be required.

It is also important to recognize functional disturbances of the gastrointestinal tract which are nonpsychogenic in origin but are secondary to primary disorders of other organs and systems such as diseases of the gallbladder, liver, pancreas, heart, kidneys, pelvic organs, endocrine glands, and the nervous system. In addition, metabolic and deficiency diseases, allergic states, and infectious and toxic conditions may give rise to functional gastrointestinal disorders.

ROENTGENOLOGY OF THE GASTROINTESTINAL TRACT

Roentgen examination is the most important laboratory aid in the diagnosis of disorders of the gastrointestinal tract. It should be performed not only in every patient in whom an organic lesion of the alimentary tract is suspected but also in those in whom functional disorders are to be detected. The various roentgen techniques include a survey film, barium meal occasionally supplemented by the insufflation of air into the stomach, small intestinal enema, special intubation techniques, and the barium water enema and barium air contrast examination of the colon.

Survey Film. A preliminary or survey film of the abdomen may sometimes furnish useful information in a variety of conditions which give rise to gastrointestinal symptoms. It may aid in the localization of calcific deposits in the pancreas, gallbladder, kidneys, mesenteric lymph nodes, and other abdominal and pelvic structures as well as in calling attention to the presence of radiopaque foreign bodies in the abdomen or the possibility of mesenteric vascular occlusion. It is useful in confirming the presence of free fluid when physical signs are not clear, and in localizing masses involving retroperitoneal structures which interfere with the clarity

of the shadows of the iliopsoas muscles. When intestinal obstruction is suspected *preliminary films* of the abdomen should be made with the patient in both the recumbent and upright positions and the films should be examined promptly for *evidence of* air or air fluid levels in the intestinal loops. Thus information not only as to the diagnosis but also as to the location of the distended loops and the site of obstruction is obtained. A survey film of the abdomen should also be made when *perforation of* a viscus is suspected. In such cases a collection of air may be found in the uppermost portion of the abdomen depending on the position of the body when examined with the beam of roentgen rays horizontal or at the site of the perforation if the latter is walled off by exudate or adhesions. The survey film is usually of no value in identifying or localizing nonobstructing lesions which involve the mucosa of the gastrointestinal tract. For this purpose a *contrast* medium is essential. Rarely an irregularity in the outline of the collection of air in the fundus of the stomach (*magenblase*) detected *in a plain film* of the abdomen or of the chest has furnished a clue to the presence of a carcinoma in *this region*.

Barium Meal. In the absence of evidence of *intestinal* obstruction or of a perforated viscus and *if the* patient is not vomiting one can proceed in most instances with the administration of a barium *meal* by mouth for the purpose of examining the esophagus stomach duodenum and small intestine and obtaining certain types of information concerning the colon. The behavior of a water barium meal and when indicated of physiologic meals containing barium should be observed fluoroscopically because the final solution of diagnostic problems often depends on a careful fluoroscopic examination. Much information can thus be obtained about the functional behavior of alimentary structures which it is not possible to get from roentgenograms. This is especially true in the detection of functional motor disturbances referred to earlier. It is important to realize however that fluoroscopic examinations vary in their reliability depending on the expertness of the observer and the care exercised by him in performing the examination. The exposure of a film offers the advantage of a permanent visual record of the lesion at any one time. The use of spot and pressure film devices is of value in the many instances when information concerning mucosal relief is desired.

If the clinical manifestations point to an obstructing or ulcerating lesion in the esophagus or stomach roentgen examination should precede passage of a tube or endoscopy as the risk of the former examination is less. It should also initiate the diagnostic survey of all patients who have recently recovered from a gastric or duodenal hemorrhage. The roentgen examination of the esophagus using capsules filled with barium and *thick and thin liquid* barium mixtures is useful in the demonstration of cardiospasm esophageal *tumors* diverticulum or ulcer hiatus hernia esophageal varices *or stricture* and nonopaque foreign bodies and to outline extrinsic mediastinal masses.

In the stomach study of the barium meal may reveal ulcer cancer polyps hypertrophic gastritis *tumors of* adjacent regions gastrojejunal ulcer and foreign bodies. *It is also useful in* detecting functional disturbances of the stomach in that it supplies information on the *characteristics of peristalsis and* tonus as well as on the *emptying time*. *Patients* with gastric ulcer under medical management should be reexamined at *the end of 3 weeks*. Persistent ulcerative lesions may require surgical intervention to rule out the *possibility of gastric* carcinoma. Lesions of the fundus of the stomach are more apt to be overlooked than those elsewhere in the stomach because of the inaccessibility of this area to palpation. The barium meal is of little value in the diagnosis of many forms of gastritis but may suggest the existence of a chronic superficial or hypertrophic gastritis. The demonstration of changes in the mucosa of the duodenal cap in cases of chronic gastritis is valuable additional evidence of the presence of gastritis. Such studies require careful evaluation of the character of the mucosal relief.

Air introduced by means of a tube is sometimes used for a contrast in the examination of the stomach. A double contrast picture may be obtained by administering a small amount of barium. This type of examination is especially useful in demonstrating polypoid tumors as well as pressure defects produced by extragastric lesions.

Fluoroscopic and roentgenographic studies of the behavior of a barium meal are of value in the diagnosis of lesions of the small intestine in the demonstration of disease in neighboring structures causing persistent displacement of a loop or loops of intestine and in revealing abnormalities in the mucosal pattern and motility. The examination of the small intestine however presents difficulties because of the overlapping loops. The duodenum and the terminal ileum are the only two segments which can be examined satisfactorily. The rapid transit of the barium meal necessitates frequent roentgen examinations. The barium should enter the cecum within 3 hr; any delay should cause suspicion. The normal mucosal pattern varies but it is affected by many factors such as emotional disturbances drugs deficiency disease inflammation adhesions constipation obstructions and neoplasms.

The study of the colon on the second day after a barium meal is not ess[illegible]

of a patient suspected of having colonic disease because it is impossible to fill the colon completely and, therefore many colonic lesions cannot be demonstrated satisfactorily The procedure however can furnish information concerning the position and functional state of the colon which may not be so satisfactorily obtained by barium enema alone It is of special value in the diagnosis of spastic colon When it is used for this purpose antispasmodics should be withheld

Small intestinal Enema Examination of the small intestine following intubation of the duodenum and the continuous gravity introduction of 500 to 1000 ml of a thin barium mixture offers many advantages in the study of the small intestine and in the diagnosis of obscure lesions The procedure permits an orderly filling of the loops from above downward and a demonstration of the entire small intestine The head of the barium column should reach the cecum in about 15 min

Intestinal Intubation The roentgen examination using the double-lumen Miller Abbott or similar tube can supply valuable information concerning small intestinal lesions and disorders Normally about 3 hr is required for the balloon to pass through the intestine into the cecum When the balloon fails to advance in 3 to 4 hr a lesion may be suspected providing sufficient slack of the gastric portion of the tube has been allowed If the inflated balloon enters the cecum an obstructing lesion of the small intestine is usually eliminated In paralytic ileus the rate of passage of the balloon is much slower than in mechanical ileus After deflation of the balloon the injection of 30 to 40 ml of a thin barium mixture at the point of its arrest may demonstrate clearly the site and the nature of the lesion causing the obstruction The barium should be withdrawn promptly after the examination is completed If surgery is decided on the tube is left in place as a guide to the point of obstruction as well as for the purpose of deflating the bowel during the postoperative period

Barium Enema The introduction of an opaque medium into the colon through the rectum is necessary in the diagnosis of organic disease of the colon For this purpose a mixture of water and barium is most commonly used The procedure is useful in demonstrating colonic tumors granulomas diverticulosis ulcerative colitis megacolon and extracolonic intraabdominal masses It is also of value in studying the terminal ileum The examination should not be relied upon to exclude lesions of the colon distal to the lower sigmoid and lesions of the rectum Diseases of these areas are best detected by proctosigmoidoscopy Small lesions involving the flexures of the colon unless carefully searched for may be readily overlooked Conditions which may contraindicate the performance of a barium enema include a painful anal fissure a tight rectal stricture in the absence of a colostomy suspected appendicitis and any acute illness in which the preparation for and the performance of the enema would prove exhausting to the patient

Barium Air Double-contrast Enema The diagnostic value of the roentgen examination of the colon may be enhanced by the introduction of air after evacuation of most of the barium The contrast furnished by the air and the barium adhering to the lumen of the bowel reveals the character of the mucosal relief Small polyps and carcinomas not seen on the usual barium enema films may be demonstrated by this method Great care and at times repeated examinations are necessary in interpreting films as retained fecal masses may be very confusing and may simulate the appearance of polyps

Roentgen examination of the gastrointestinal tract is not an infallible procedure Lesions may be missed even by those with great skill and much experience Consequently when the clinical evidence indicates the possibility of serious disease and the roentgen study is negative the examination should be repeated The need for multiple or repeat examinations to discover an early carcinoma of the stomach or a polyp of the colon is not generally appreciated

OTHER DIAGNOSTIC METHODS

Endoscopy as well as methods such as liver function tests and other procedures will be discussed in context.

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242 DISEASES OF THE MOUTH

Thomas E Machella

Careful inspection of the mouth often yields important information Aside from the signs of various local diseases of the oral structures which

will not be discussed in this book significant evidence of systemic disturbances is often encountered Of the disorders which frequently produce abnormalities in the mouth the following are especially important

Disturbances of Fluid Balance These have been discussed in some detail in Chap 48 Dryness of the mucous membrane and a longitudinal wrinkling of the tongue are likely to be indications of water deficit and extracellular fluid deficit respectively Dryness of the mucous membranes may also be encountered in mouth breathers or constant talkers and as a part of the idiopathic state known as *Sjogren s syndrome* Increased salivation or ptyalism may be observed in patients with excess fluid intestinal parasites mercury poisoning postencephalitic form of parkinsonism scurvy hyperchlorhydria iodism and cretinism

Hematopoietic Disorders Pallor of the mucous membranes is a better index of anemia than is pallor of the skin Atrophy of the papillae of the tongue with loss of the characteristic dorsal granularity is observed in most patients with pernicious anemia and in occasional instances of chronic hypochromic anemia A bright red sore tongue may be seen in pernicious anemia A deep maroon color instead of the normal reddish pink of the oral surfaces is typical of polycythemic disorders Hemorrhagic spots on the palate and cheeks are common in the more severe thrombocytopenic purpuras both primary and secondary Edema swelling and often ulceration and necrosis of the gum may occur in acute leukemia and there may be a hypertrophic gingival reaction These are readily differentiated from the hypertrophy of the gums following prolonged use of Dilantin (diphenylhydantoin sodium) for epilepsy Pain marginal necrosis and bleeding are absent in the latter Necrotic ulcerative irregular shaped sores of the mouth and pharynx may be found in cases of granulocytopenia

Nutritional Disorders The tongue is characteristically deep red (beefy) in patients with pellagra and in many patients with sprue as a result of a deficiency of one or more members of the vitamin B complex such as nicotinic acid or riboflavin A superficial glossitis may also accompany a chronic iron deficiency anemia with or without other manifestations of the Plummer Vinson syndrome Spongy swollen and purple-red gums which bleed readily are observed in advanced scurvy provided the patient has natural teeth

Endocrine and Metabolic Disorders Bronze colored spots of pigmentation on the buccal mucous membrane of the cheeks and palate are suggestive of Addison s disease although somewhat similar areas may be seen in patients with hemochromatosis The tongue is likely to be large and in persons with myxedema Macroglossia may also be observed in acromegaly and in primary systemic amyloidosis Soreness and burning of the tongue without obvious change in appearance may be a manifestation of diabetes though actual lesions of the gums and tongue are not uncommonly found in diabetic patients because of the predisposition to infection Recurring or cyclic ulcerative stomatitis in association with vulvitis ascribed to ovarian dysfunction has responded to gonadotropin administration Similar changes in the mouth may occur in erythema multiforme

Metallic Poisoning Granular black pigmentation of the gums at the points of insertion of the teeth and diffuse reddening of the oral mucous membranes with profuse salivation are suggestive of intoxication with lead and mercury respectively A stomatitis and gingivitis with bluish pigmentation may be observed in patients receiving bismuth therapy and a gingivitis from exposure to chromium Dryness of the mouth may be complained of in zinc poisoning

Other Disorders Numerous alterations of the oral cavity may occur Among the more characteristic are the strawberry tongue" of scarlet fever the Koplik spots of measles the membranous patches of diphtheria the vesicles of smallpox and chickenpox the heavily coated tremulous tongue of typhoid fever the chancre of primary syphilis the mucous patches of secondary syphilis and the bald tongue of tertiary syphilis Also to be borne in mind are the aphthous ulcers and swollen bleeding gums of herpes simplex and the papular vesicular and ulcerative lesions of herpangina Ulcers in the mouth are a very common presenting lesion in histoplasmosis Less commonly encountered are such miscellaneous infections as blastomycosis leprosy leishmaniasis and lymphogranuloma venereum Stomatitis occurs in uremia and following the administration of broad spectrum antibiotics especially chloramphenicol Hairy tongue often follows the use of penicillin lozenges Any indolent lesion in the mouth merits biopsy to rule out malignancy

243 DISEASES OF THE ESOPHAGUS

Franz J Ingelfinger

Although the anatomy of the swallowing tube is still controversial the structural definitions indicated in Fig 170A are used in this discussion The esophagus proper with principally propulsive functions is regarded as lying between two sphincteric segments at its upper and lower ends The upper

segment comprises the cricopharyngeus muscle and the highest circular muscles of the esophagus The lower sphincteric mechanism is considered to depend on a zone including the inferior esophageal sphincter and a portion of the vestibule It normally remains closed except during swallowing or regurgitation and with the diaphragm is instrumental in preventing gastric reflux.

Symptomatology ***Dysphagia*** Although esophageal disease accounts for no more than one tenth of all gastrointestinal complaints it is characterized by one of the most specific symptoms in medicine the sensation of food sticking on its way from the mouth to the stomach This dysphagia of esophageal origin must be clearly distinguished from the swallowing difficulties caused by inability to expel material from the oropharynx into the esophagus Esophageal dysphagia since it occurs only with swallowing also differs from the persistent sensation of globus hystericus Esophageal dysphagia may be painless more often it is distressing and sometimes it causes pain of alarming proportions Whatever its concomitants the complaint of food sticking somewhere behind the sternum signifies that some process—whether functional spasm or organic stricture—is occluding the esophageal lumen

The level of the sticking sensation, corresponding to the most frequent site of esophageal disease is usually under the lower end of the sternum In other instances dysphagia is localized higher in the chest or at the base of the neck either because the responsible lesion is situated higher or because sensations from the distal esophagus are referred to the sternal notch by approximately one fourth of adult patients

Dysphagia occasionally begins abruptly and reaches maximum intensity at the onset but more commonly it appears gradually in intermittent attacks precipitated by the ingestion of certain foods Beef and fresh bread are notorious offenders probably because these elastic solids are wedged by peristalsis into the esophageal area narrowed by disease If this happens the patient may be able to force the offending morsel past the obstructing point by rapidly gulping water With progressive disease however the swallowing of liquid as well as solid becomes difficult. Liquids of low viscosity as a matter of fact, are regurgitated too readily and the peristaltic action of the esophagus is used to best advantage when the patient takes food of pultaceous consistency

Pain. Pain, a common symptom of esophageal disease may be persistent and unrelated to swallowing or intermittent and intimately associated with dysphagia often it is precipitated by the ingestion of acid, spicy carbonated very cold, or very hot substances The mechanisms underlying esophageal pain are two (1) ulceration or inflammation of the mucosa and (2) increased intramural tension produced by violent peristalsis or stationary muscular spasm Esophageal pain is usually felt anteriorally under the sternum at a level corresponding to the position of the lesion but it may also be referred to the upper back the neck the jaws and into both arms particularly their inner aspects Anatomically and functionally therefore the transmission and reference of pain from the esophagus and from the heart may be the same

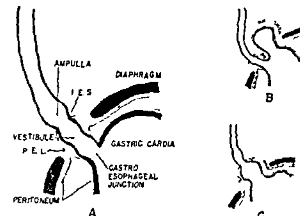


Fig 1?0 Diagrammatic representation of the structure and relations of the lower esophagus A Normal esophagus B Parahiatal hernia C Sliding hernia In this type of hernia the distinction between the vestibule and the herniated cardia is lost I E S = Inferior esophageal sphincter P E L = Phrenoesophageal ligament (*Modified from Lerche Allison and Sweet*)

Heartburn Heartburn pyrosis and water brash mean different things to different people and it is important to determine what *heartburn* signifies to the patient with this complaint Here the term *heartburn* is used to denote an intermittent symptom complex which begins with a burning, tight sensation under the sternum and then travels upwards wavelike to reach its scalding, acid maximum in the neck or throat Salivation is often part of the picture The cause of heartburn may be muscular spasm reflux of gastric contents or both but its exact pathogenesis is still uncertain.

Belching Many a belch is forceful regurgitation of air that has been sucked or swallowed into the esophageal lumen Although belching, therefore is frequently an esophageal phenomenon it is except in diaphragmatic hernia, not a common manifestation of esophageal disease More often it is a functional disorder or is indicative of gastric or cardiac disease

Regurgitation. Regurgitation, as opposed to vomiting, means the effortless appearance of esophageal or gastric contents in the mouth A functional disorder of esophageal motility a retrograde

flow of material forced by normal esophageal peristalsis against a stenotic area or as in the case of the dilated esophagus of cardiospasm a gravitational effect may be responsible for regurgitation

CANCER

Symptoms The importance of dysphagia as a symptom and the urgent necessity of determining its cause are no better exemplified than by the patient with esophageal cancer Difficulty in swallowing is often the patient s first and at times his only complaint as the growth encroaches upon the lumen Although intermittent initially the dysphagia is inexorably progressive over the course of months In fungating tumors the commonest gross variety of esophageal cancer pain under the sternum in the back or in the neck makes its appearance sooner or later In some cases an early symptom not to be ignored is substernal burning on swallowing hot liquids Slow oozing of blood is a frequent complication and brisk bleeding a rare one In about 25 per cent of cases however particularly with infiltrative or polypoid cancers symptoms other than dysphagia appear only terminally When esophageal stenosis is severe regurgitation of esophageal contents sometimes blood flecked is common

Approximately 20 per cent of esophageal cancers are in the upper third 30 per cent in the middle and 50 per cent in the lower third of the organ The lesions in the upper two thirds are derived from squamous esophageal mucosa In the distal esophagus over half the cases prove to be adenocarcinomas indicating that many cancers in this area are gastric in origin A gastric origin is as a matter of fact often evident on operation in cases which radiologically appear to be purely esophageal

Course Physical examination is usually negative and even those in an advanced state may present no more than the signs of malnutrition Although metastases to lymph nodes occur in three fourths of the cases only 5 per cent have palpable nodes in the supraclavicular or other accessible areas Since the liver and lung are each involved eventually in 20 to 25 per cent of the cases hepatomegaly or pulmonary lesions may be evident Other organs subject to metastatic foci are bone kidneys and adrenal gland Sometimes direct invasion of adjoining structures leads to dramatic complications (1) mediastinitis with subcutaneous emphysema in the neck (2) tracheo or bronchoesophageal fistula with an apoplectic cough induced by swallowing liquids or (3) aortic perforation with precipitous exsanguination

Diagnosis Esophageal cancer occurs in the usual cancer age groups and males preponderate four to one It is about one tenth as common as cancer of the stomach in either sex X ray often reveals the irregular and sometimes surprisingly long luminal defect caused by esophageal cancer but other invaluable information is provided by esophagoscopy and biopsy The initial examination with either procedure is not however invariably adequate in differentiating cancer from inflammatory stricture Cytologic examination of material obtained by esophageal lavage is proving remarkably helpful

Treatment Intensive deep radiotherapy such as has been made available by high voltage x ray apparatus and Co^{60} bombs is achieving some palliative success but lesions that appear to be resectable are usually treated surgically Calculated on the basis of all esophageal cancer patients who enter a hospital the 5 year cure rate is still a disappointing 0 to 7 per cent In some hands however 5 year cure rates in patients who at operation have no gross evidence of extension are over 30 per cent for cancers in the lower third of the esophagus Successful resection of higher cancers is more difficult

DIAPHRAGMATIC HERNIA

A common abnormality affecting the esophagus but strictly speaking of gastric origin is herniation of the stomach through the esophageal hiatus of the diaphragm Two types of hernia are described In one the paraesophageal or parahiatal type the gastric cardia slips through the muscular aperture beside a normally situated gastroesophageal junction still encircled by the fibrous components (the phrenoesophageal ligament) of the hiatus (Fig 170B) In the other the sliding or short-esophagus type the stomach slides through both the membranous and muscular openings thereby placing the gastroesophageal junction above the diaphragm (Fig 170C) This position of the junction makes the esophagus appear shortened and actual shortening may be caused by chronic esophageal inflammation A congenitally short esophagus however is very rare

The incidence of diaphragmatic hernia is debated since its radiologic differentiation from a prominent vestibule is a matter of individual interpretation In elderly people however the incidence may be as high as 33 per cent and stocky obese patients are particularly susceptible The relative prevalence of the two types of herniation is also uncertain but symptoms arise more commonly from the sliding type

Symptoms Both parahiatal and sliding hernias may give rise to symptoms when the herniated pouch is irritated or injured by the mechanical disadvantages of its position or when it is sufficiently large to affect adjoining viscera These complications appear to be especially prevalent in women

The most common complaint is high epigastric or low midthoracic pressure or a pain which may radiate along the left costal margin to the top of the left shoulder or down the arms. Belching is copious and hiccoughing occasional. By and large the symptoms are moderately distressing but a rare case may suffer acute prostration should strangulation of the herniated stomach take place. If the mucosa of the hernia becomes eroded acute or chronic blood loss is possible but the importance of diaphragmatic hernia as a source of gastrointestinal blood loss is usually exaggerated. Large hernias rarely cause intermittent acute dysphagia by angulating, twisting or compressing the esophagus or they may sufficiently displace the lungs or heart to cause cardiorespiratory symptoms. Whatever the clinical manifestations of diaphragmatic hernia they are characteristically precipitated by eating and aggravated by lying down both of which actions tend to force more of the stomach into the thoracic cavity.

The principal complication affecting sliding diaphragmatic hernias is peptic esophagitis. This is discussed below.

Diagnosis. Diagnosis is made by radiologic means. Once a diaphragmatic hernia is radiologically identified however its relation to the patient's symptoms poses a nice problem. On one hand the symptoms of diaphragmatic hernia are so diverse that they may resemble the symptoms of coronary insufficiency, biliary colic, pancreatitis, gastric or duodenal ulcers, esophageal diseases (Table 122) or functional digestive disorders. On the other hand, diaphragmatic hernias are diagnosed so frequently by the radiologist that many hernias must be considered as incidental findings unrelated to the patient's complaints. As a rule upper abdominal or lower thoracic symptoms should not be ascribed to a radiologically demonstrated diaphragmatic hernia unless (1) other possible causes are excluded with reasonable certainty and (2) some evidence exists that the symptoms are intensified when the patient eats or lies down. A particularly difficult problem in differential diagnosis is substernal distress in the elderly patient with both electrocardiographic abnormalities and diaphragmatic hernia. Although coronary pain is usually related to exercise and that of hernia precipitated by lying down these associations are not constant and both conditions may be aggravated by a full meal. When the evidence is conflicting the wiser course is to assume that coronary disease is the principal offender.

Treatment. Most patients can become fairly comfortable but not entirely symptom free by eating small meals of low fat content (fat retards gastric evacuation) by avoiding food entirely for 3 hr before going to bed and by sleeping with the upper half of the body elevated. Additional symptomatic relief may be afforded by sedatives and antispasmodics. With respect to surgery sliding hernias with esophagitis present a special problem but the approach to paraesophageal hernias should be extremely conservative. Operative repair of these hernias is not indicated unless they have been identified unquestionably as causing intermittent esophageal obstruction, respiratory disease, perforation, strangulation, bleeding or severe distress not affected by intensive use of medical measures. In some cases major surgery can be avoided and symptoms lessened by crushing the left phrenic nerve to paralyze the left diaphragm.

ACUTE ESOPHAGITIS

Acute esophagitis in a mild form with substernal pain aggravated by swallowing may complicate upper respiratory infections. More violent forms with variable necrosis may occur in moribund states, in diseases of the central nervous system, after extensive burns or trauma, after operations especially if vomiting is pronounced or gastric intubation prolonged, and with specific infections such as scarlet fever, diphtheria and typhoid. In many of these conditions ischemia, the trauma of vomiting and exposure of the esophageal mucosa to acid gastric contents must be important pathogenic factors.

The ingestion of corrosive agents produces a classic variety of acute esophagitis which if not immediately fatal commonly terminates in extensive esophageal stenosis.

CHRONIC ESOPHAGITIS

Chronic esophagitis is an inflammatory reaction of the esophageal wall with erosions or frank ulceration of the mucosa and narrowing of the lumen by muscular spasm and fibrotic stricture. This chronic disorder has been reported as a sequel to acute esophagitis as a complication of systemic or local diseases and as a late radiation effect but from the long list of heterogeneous and often obscure causes reflux of gastric contents is probably the most significant.

Peptic esophagitis and the acid peptic factor appear to be causally related since this form of chronic esophagitis occurs predominantly in males and over one third of the cases have or have had duodenal ulcer. In addition patients affected have a sliding diaphragmatic hernia or a history of prolonged gastric intubation or vomiting, circumstances suggesting that the acid peptic factor gains access to the esophagus because normal mechanisms preventing gastric reflux are impaired. In some adults and more commonly in infants or children severe

Table 12? DIFFERENTIAL DIAGNOSIS OF ESOPHAGEAL DISORDERS

Disorder	Symptoms (in order of incidence)	Dysphagia		Blood loss	X-ray	Esophagoscopy	
		Chronology of development	Sensation of food working through obstructed area			Insertion of instrument past narrowed area	Purpose and significance
Cancer	1 Dysphagia 2 Pain—70% of cases	Weeks to months	Yes (early in course)	Intermittent oozing common Brisk bleeding rare	Normal peristalsis Mild dilatation Irregular defect Diaphragm Gastric cardia	Difficult or impossible	Essential examination for inspection and biopsy in all suspicious cases. Not indicated when x-ray diagnosis of cancer appears unequivocal since risk of procedure unnecessary
Diaphragmatic hernia (paraesophageal)	1 Epigastric or substernal pressure 2 Belching 3 Intermittent attacks of pain 4 Dysphagia either absent or occurs in rare and transient attacks	Months to years	No	Alleged common cause of acute and chronic bleeding, but incidence exaggerated	Normal esophagus except for displacement by Herniated stomach Diaphragm	Readily accomplished	Little additional information obtained
Peptic esophagitis	1 Heartburn 2 Substernal pain after cold, hot, spicy, and acid food 3 Dysphagia 4 History of peptic ulcer—30% of cases	Months to years	Yes	Hemorrhage occur but unusual	Dilatation absent to moderate Funnel-shaped narrowing of stricture Possible ulcer niche Sliding gastric hernia	Difficult or impossible	Important examination to evaluate esophagitis and exclude cancer. Frequently used as ancillary procedure in dilatation of stricture
Cardiospasm	1 Dysphagia 2 Occasional attacks of pain 3 Regurgitation 4 Chronic cough	Years	Infrequent	None except after operative procedure leading to secondary esophagitis	Dilated esophagus Irregular uncoordinated contraction Beak-shaped narrowing produced by achalasia of vestibule	Surprisingly easy except in case with such massive esophageal dilatation that the distal lumen cannot be identified	Helpful to evaluate secondary esophagitis and to carry out dilating procedure

peptic esophagitis may be related to abnormal extension of gastric mucosa into the esophagus

Symptoms The patient may or may not have had a past history of duodenal ulcer but almost invariably he has been a long sufferer from heartburn At first this symptom troubles the patient only after dietary indiscretions soon after retiring to bed, or when bending over Intermittently and progressively however the heartburn worsens cold and hot foods and slightly acid foods are increasingly painful to swallow and eventually dysphagia appears With advancing disease malnutrition is inevitable and slow blood loss occasional

Diagnosis Diagnosis is made principally by x ray which in cases with stricture shows a gradual and funnel shaped narrowing of the distal esophagus The esophagus appears shortened and terminates in a tentlike supradiaphragmatic projection of the stomach characteristic of a sliding hernia The differential diagnosis is outlined in Table 122 but examination of cells obtained by biopsy esophageal washings, or both is essential

Treatment Medical treatment has a twofold aim reduction of gastric acidity and prevention of gastric reflux. To these ends the patient should observe an intensive ulcer regimen modified to the extent that he should avoid foods (but not antacids) after the evening meal and should sleep with the upper half of his body elevated Anticholinergics may be helpful at bedtime to reduce nocturnal gastric secretion, but they are best avoided during the day since anticholinergics increase gastric retention and reduce the gastric secretory response to meals but little Medical management may relieve dysphagia produced by spasm but it is relatively ineffective when the cause is a well-defined stricture This is treated by cautious dilatation

If dysphagia persists or recurs in spite of medical treatment surgical intervention is indicated In an early case repair of the sliding hernia may be sufficient but in most instances some type of operation designed to reduce gastric acidity (subtotal gastrectomy vagotomy *with* a drainage procedure) is carried out at the same time Such surgical effort is unfortunately not much more than 75 per cent successful Resection of the involved area as may be necessitated by uncontrollable stenosis is also not too rewarding since all barriers to gastric reflux are removed recurrence of esophagitis proximal to the gastroesophageal anastomosis is likely Some surgeons are trying to overcome this difficulty by replacing the resected esophageal section with a segment of small intestine

PEPTIC ULCER

A solitary peptic ulcer is occasionally found in the distal esophagus This lesion differs from peptic esophagitis in that the ulcer is more sharply localized penetrates more deeply and is more apt to perforate or to cause massive bleeding On the other hand the ulcer is more susceptible to standard medical antacid management (Chap 245) produces less extensive stricture on healing and causes less chronic dysphagia than peptic esophagitis The solitary peptic ulcer in the distal esophagus thus resembles a benign gastric ulcer in many respects Indeed many ulcers at the lower end of the gullet actually involve either a herniated portion of stomach or a section of the esophagus—perhaps the vestibule—that is lined with gastric mucosa

CARDIOSPASM

The term *cardiospasm* does not describe the nature of the disorder accurately but is well established by custom Actually cardiospasm is a motor disorder involving the entire distal two thirds of the esophagus In the esophagus above the vestibule the normal propulsive pattern of peristalsis is replaced by nonprogressive and uncoordinated contractions For this reason the name *aperistalsis* is used in Brazil The massive esophageal dilatation seen in some cases has in turn given rise to the name *megaesophagus* Finally the term *achalasia* (literally "not relaxation") is popular because the lower esophageal sphincter i e the vestibular area does not relax normally in response to swallowing and thus creates an obstructing segment at the distal end of the esophagus

The motor disorders of cardiospasm appear to reflect an impaired cholinergic innervation of the esophagus Histologically the cells of the myenteric plexus i e the parasympathetic ganglions are damaged or absent Pharmacologic studies have shown that administration of a cholinergic agent produces a tetanic specific and often violent contraction of the affected esophagus This response when interpreted in the light of Cannon s finding that denervated structures respond maximally to neurohumoral stimulation provides additional evidence that the cholinergic innervation of the esophagus is deficient in cardiospasm The ultimate etiology however is unknown

Symptoms Cardiospasm affects all ages of both sexes Its course is usually chronic with dysphagia gradually worsening over months to years In some patients the process is painless in others spasms of substernal pain may follow eating Occasionally the initial episode of dysphagia appears with dramatic suddenness either after bolting food or after an emotional upset In either case however the condition has probably been present in latent form before the acute episode As the disease progresses extreme and tortuous dilatation of the esophagus may develop When the patient lies down the

copious amount of food residue saliva and other secretions contained in the spacious esophageal sac runs freely back into the pharynx and mouth If the regurgitated material is aspirated chronic infection of the lung bases is a potential complication Stagnation of food also leads to a chronic inflammatory reaction of the esophageal mucosa and submucosa Obviously weight loss is common

Diagnosis Diagnosis is usually made without difficulty on the basis of the history and the characteristic radiologic findings of abnormal esophageal motor function with a smooth beaklike narrowing of the distal esophageal segment (Table 122) In some cases cancer originating in the gastric cardia but infiltrating the esophagus may present a somewhat similar x ray appearance and a variety of motor disorders of the lower esophagus has been confused with cardiospasm These problems in differential diagnosis should be less frequent if it is remembered that the radiologic abnormalities of cardiospasm consist of deranged peristalsis as well as narrowing in the area of the vestibule

Treatment Medical treatment symptomatic at best consists of the use of sedatives and bland semisolid foods warmed to body temperature Smooth muscle relaxants such as nitrites are often used to open the vestibule but the effect is too transient to permit the patient to enjoy a meal Anticholinergics may lessen oral and esophageal secretions and may inhibit painful spasms in view of the basic neurologic defect however they potentiate rather than alleviate the dysphagia The best available therapy is forceful dilatation of the narrowed vestibule with the specific purpose of tearing some of the muscle fibers in this area Passing graduated mercury tipped bougies does not accomplish this and therefore relieves dysphagia only briefly It is necessary to use bags that can be inflated under pressure or a mechanical (Starck) dilator In experienced hands these instruments when positioned under fluoroscopic control rarely cause complete esophageal rupture and dysphagia is relieved successfully for years or even permanently in over 75 per cent of cases Forceful dilatation does not restore normal esophageal motility but it impairs the contractile power of the vestibule and thus permits the esophagus to empty under the influence of hydrostatic and transmitted oropharyngeal pressures Improved esophageal emptying in turn prevents further esophagitis and distention of the lumen

When the esophagus is extremely dilated and sufficiently tortuous to warrant the adjective *sigmoid* mechanical dilatation of the narrowed area is often not feasible Surgery is then necessary Unfortunately any procedure that creates a new opening between the dilated esophagus and the stomach permits when the patient lies down reflux of gastric contents into an already damaged esophagus which cannot muster the peristaltic force necessary to return the gastric contents where they belong The consequence is severe esophagitis often more distressing than the cause of the operation and a major source of blood loss If technically feasible the surgical procedure favored at present is the Heller myotomy which is based on the same principle as forceful dilatation the contractile power of the vestibule is destroyed by placing a longitudinal cut through the muscle but not the mucosa of the narrowed segment Myotomy is however not invariably successful in alleviating dysphagia or preventing reflux esophagitis The lesson is plain once cardiospasm is diagnosed forceful dilatation of the vestibule should be carried out promptly to prevent the progressive enlargement of the esophagus that eventually requires major surgery

DIVERTICULA

Diverticula are found in the esophagus in about 5 per cent of older patients who are given a swallow of barium Most of these pouches occur in the mid and distal esophagus but they are usually small (1 to 4 cm in diameter) and do not cause symptoms Extremely rarely an esophageal diverticulum is subject to ulceration or becomes large enough to cause dysphagia A diverticulum of great clinical importance however is Zenker s diverticulum a pouch which actually arises in the posterior aspect of the hypopharynx but which extends downward between the spine and the esophagus Patients with this condition—elderly males for the most part—suffer dysphagia because swallowed material tends to fill the diverticular sac which then compresses the esophagus Regurgitation of food fouled by stagnation and nocturnal fits of coughing may complicate the picture Diagnosis can usually be made by x ray provided the pharynx is adequately studied as the patient swallows barium Surgical treatment is necessary to relieve the symptoms of a Zenker s diverticulum but may be complicated by mediastinal infection disorders of pharyngeal function during swallowing or recurrence of the diverticulum

OTHER ESOPHAGEAL DISORDERS

Disorders of Motor Function In elderly people normal peristalsis in the lower esophagus above the vestibule may be replaced by so called curling a type of motility which on radiologic study imparts a peculiar beaded appearance to the contracting organ The condition is usually asymptomatic but may be confused radiologically with esophageal varices Rarely the abnormality is sufficiently severe to cause dysphagia The disorder is then known

as *diffuse spasm of the esophagus* or *corkscrew esophagus* because the contracting esophagus appears by x ray to have assumed a bizarre corkscrew pattern

The *lower esophageal ring* is a thin symmetrical annular narrowing located 1 to 4 cm above the diaphragmatic hiatus The ring may be muscular (inferior esophageal sphincter?) or a membranous web but is probably not congenital as it is found more commonly in older patients Five to ten per cent of adults have asymptomatic rings but if the residual lumen is less than 12 mm in diameter the ring may cause a highly characteristic syndrome consisting of intermittent attacks of dysphagia recurring over years unassociated with any other esophageal abnormality and invariably precipitated when the patient swallows meat or other elastic chunks without proper chewing Treatment consists of avoiding such haste

In infants with *chalasia* the normal tonic contraction of the lower sphincter between swallows is absent and free regurgitation from the stomach occurs The condition also affects an occasional adult

About 20 per cent of patients with *scleroderma* suffer esophageal involvement with moderate dilatation of the lumen absent motor function and variable dysphagia In doubtful cases the esophageal changes may be the means of diagnosing scleroderma

Perforation and Rupture Perforation of the esophagus may complicate esophagitis peptic ulcer or neoplasm Rupture may be induced by external trauma or more commonly during instrumentation of the esophagus Sometimes it develops spontaneously in a previously healthy organ The consequences are a syndrome comprising (1) severe pain, usually substernal but occasionally epigastric or precordial and intensified by swallowing (2) free air in the mediastinum producing a mediastinal crunch (Hamman s sign) and subcutaneous emphysema palpable within 1 to 12 hr above the collarbones (3) digestion of mediastinal pleura by pressure and gastric juice with resultant hydro or hemopneumothorax and respiratory embarrassment (4) shock and (5) secondary infection

Spontaneous rupture is a specific entity that develops suddenly during vomiting or coughing, or occasionally merely after injudicious gluttony The tear 1 to 8 cm in length almost invariably is in the posterolateral portion of the esophagus immediately proximal to the diaphragmatic hiatus The diagnosis is to be suspected in elderly males (60 per cent of cases) who are suddenly seized by the typical syndrome while vomiting or coughing it is established by x ray (air in mediastinum or neck, demonstration of laceration by having the patient swallow radiopaque oil pleuropulmonary abnormalities) thoracentesis revealing gastric contents and exclusion of myocardial infarction, pancreatitis and ruptured abdominal viscus Air under the diaphragm is never found in spontaneous esophageal rupture

Perforation or rupture of the esophagus is highly lethal In most cases but particularly those of instrumental or spontaneous rupture of a previously normal esophagus immediate surgical repair of the rent is crucial If surgical repair is not delayed, the mortality of spontaneous rupture can be reduced to 33 per cent

A disorder closely allied to spontaneous esophageal rupture is vertical laceration of the gastroesophageal junction producing, since local vessels are involved severe and usually exsanguinating hemorrhage This so-called *Mallory Weiss syndrome* usually develops when prolonged vomiting follows an alcoholic bout

Foreign Bodies Foreign bodies may cause dysphagia, pain, or perforation of the esophagus Rigid bodies usually are arrested above the aortic arch and elastic material in the distal esophagus Not infrequently a structural abnormality or disease of the esophagus is responsible for stopping the foreign body

Varices Esophageal varices are discussed in Chap 18 p 150 and Chap 250 p 1501 They do not cause dysphagia or other esophageal symptoms Radiologically however their appearance may be confused with that of cancer or esophagitis

Congenital Esophageal Atresias and Fistulas Such atresias often associated with fistulas communicating with the respiratory tract, are found in infants Since these disorders are practically invariably problems of earliest infant life the reader is referred to standard texts on pediatrics for details

Plummer Vinson Syndrome This syndrome is a cause of dysphagia in women with hypochromic anemia Sometimes a pseudoweb is seen in the cricopharyngeal area sometimes mucosal inflammation or atrophy and sometimes no endoscopic or radiologic abnormality whatsoever A good diet and iron are therapeutic

The esophagus is in rare instances affected by the following conditions papilloma, adenoma leiomyoma, cyst leukoplakia, acanthosis nigricans sarcoma and lymphoma

Specific Infections Specific infections which occasionally attack the esophagus are tuberculosis syphilis actinomycosis and thrush.

Extrinsic Disease Diseases of the aorta, heart respiratory tract or mediastinal lymph nodes often displace the esophagus and may appear to narrow the lumen, at least in one diameter Aneurysms of the aortic arch may compress the esophageal lumen against the spine otherwise however dysphagia is rarely produced by extrinsic esophageal masses

and invasion of the esophagus by mediastinal cancer or sarcoma is extremely uncommon

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For further discussion of problems considered in this chapter the reader is referred to Chap 4 Pain in the Chest and Chap 15 Indigestion Dysphagia Nausea and Vomiting

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244 DISEASES OF THE STOMACH

Seymour J Gray

The gastrointestinal tract has often been referred to as the sounding board of the emotions and as such is subject to a host of neurogenic secretory motor hormonal endocrine and vascular influences It must in addition contend with the daily bombardment of exogenous irritants thermal and bacterial variants and mechanical factors

The original observations of Beaumont in 1833 and the later ones of Wolf and Wolff demonstrated the close relationship between emotional disturbances vascular responses increase in gastric secretion and ulcer formation

New vistas appeared through the efforts of Freud Pavlov and Cannon into the mechanisms by which emotional disturbances may reach the stomach The hypothalamus was shown by Cannon to be the seat of primitive emotions probably under *control of centers within the frontal lobe* according to Fulton Emotional and physical duress or injury may stimulate the hypothalamic centers either by neural pathways from the higher centers in the brain or by substances liberated as a result of stress

The neurogenic concept of gastric disease began with Rokitansky in 1842 who postulated a relationship between the stomach and the brain Later Cushing in 1932 demonstrated that stimulation along the course of the fiber tracts from the anterior hypothalamus to the vagal centers produced gastric ulcerations and erosions accompanied by hypersecretion hypermotility and hypertonus

Studies have indicated that chronic emotional and physical duress may also be mediated to the stomach by a pure hormonal pathway through the hypothalamus pituitary and adrenal glands which is independent of the vagus nerve

An understanding of the significance of emotional disturbances is essential to the clinical evaluation of the patient with gastrointestinal complaints The high incidence in the population at large of both gastrointestinal disease and psychologic disorders makes coincidence very common and presents the physician with the challenge to separate the psychologic from the organic components of the history

The physician must be armed with a strong suspicion of malignancy in view of the absence of the classical signs and symptoms" of gastric cancer in 75 per cent of instances until the patient is riddled with metastases The history of early cancer may not differ superficially from that of gastritis or peptic ulcer "Pylorospasm has become a catch all for many types of indigestion" in spite of the fact that pylorospasm per se probably causes no distress unless it is associated with an underlying ulcer gastritis or malignancy

In eliciting the history the physician should investigate recent changes in the character of the distress by outlining a typical day" to determine the hour by hour pain pattern with reference to meals or relief by food or antacids A recent decrease in food intake may signify an early malignancy Inquiry into the family background of gastric cancer or peptic ulcer is helpful but not conclusive A history of tarry stools or hematemesis suggests peptic ulcer gastritis or esophageal varices rather than gastric malignancy Since many organic processes manifest themselves with gastrointestinal complaints inquiry into diseases of the heart and coronary vessels gallbladder kidney and pelvic organs is essential

The nonspecificity of many gastrointestinal complaints emphasizes the importance of integrating a

meticulous history and physical examination with carefully selected laboratory procedures Repeated search for occult blood in the stools by the newer benzidine dihydrochloride method should constitute part of every routine examination The finding of unexplained persistent occult blood by this sensitive test warrants further investigation for malignancy Its use as a screening procedure for cancer is indicated in (1) patients over forty with any gastrointestinal complaints (2) pernicious anemia (3) gastric polyps (4) histamine proved gastric anacidity and (5) gastric ulcer Persistent occult blood in the gastric ulcer patient after 3 to 4 weeks of treatment may indicate malignancy The string test to be described later is helpful in determining the presence and site of upper gastrointestinal bleeding

The histamine test is the most simple reliable and reproducible method of measuring the free hydrochloric acid secretion of the stomach Its principal use is in evaluating *anacidity* rather than degree of hyperacidity Anacidity to histamine stimulation is the best evidence of true anacidity and is important in the diagnosis of (1) pernicious anemia, (2) gastric polyps and (3) gastric cancer Anacidity occurs in 60 to 70 per cent of all gastric cancer patients and in the presence of a *gastric ulcer* is presumptive evidence of cancer since free acid after histamine is almost always present in benign ulcer although it is often *lower* than normal The presence of high acid does *not* exclude cancer Routine gastric analysis is unnecessary in duodenal ulcer since the acid level in any individual patient is not significant diagnostically although the *average* secretion is considerably higher than normal The demonstration of very high values however may be a guide in the treatment

Other newer methods of investigating the gastric contents directly or indirectly include (1) exfoliative cytologic examination for tumor cells obtained with the abrasive balloon or after gastric lavage with chymotrypsin (2) uropepsin excretion in the urine which is a measure of gastric pepsin and (3) urinary test for free gastric acidity with the quininium or azure A exchange indicator compounds

The roentgen examination is indispensable in the diagnosis of gastric disease and is indicated in all patients over forty with epigastric distress The procedure is used most extensively to (1) exclude gastric malignancy (2) establish a diagnosis of peptic ulcer and (3) determine response to treatment, particularly in gastric ulcer if lack of healing suggests malignancy Other indications for roentgenography include (1) persistent occult blood in the stools (2) massive gastric hemorrhage (3) unexplained anemia (4) pernicious anemia (once yearly) and (5) gastric polyps Accuracy of diagnosis approximates 90 per cent

Gastroscopy offers direct visual inspection of the interior of the stomach and is indispensable for the diagnosis of gastritis where roentgen studies are usually nonspecific Additional indications include (1) differential diagnosis of benign and malignant ulcer (2) gastrointestinal bleeding of undetermined origin (3) visualization of small polyps particularly in pernicious anemia (4) evaluation of questionable roentgen findings (5) identification of the type and extent of malignant lesions and (6) identification of foreign bodies The examination is contraindicated in esophageal disease with obstruction extensive esophageal varices severe pulmonary or mediastinal disease aortic aneurysm perforated peptic ulcer peritonitis and marked scoliosis Patients with angina pectoris cardiac decompensation and hypertension tolerate the procedure quite well Gastroscopy should always be preceded by roentgen examination of the chest, esophagus and stomach

Limitations of the procedure are (1) technical problems with incomplete visualization of the lesion (2) difficulties in interpretation and (3) blind areas" which include a small strip of the posterior wall in contact with the instrument a small portion of the lower pole of the stomach the lesser curvature of the antrum and part of the cardia immediately adjacent to the objective

Gastric biopsy obtained with an operative gastroscope or by a flexible vacuum tube inserted into the stomach has contributed further to the diagnosis of gastric disease

GASTRITIS

Gastritis may be defined as an acute or chronic inflammation of the stomach nonspecific in nature involving one or more layers of the gastric mucous membrane

The clinical significance of gastritis stems from its relationship to peptic ulcer pernicious anemia gastric polyps and cancer of the stomach and its tendency to produce ulcerlike symptoms and massive gastric hemorrhage

Acute Gastritis

Irritants and infections are the most common causes of acute gastritis Emotional disturbances may initiate superficial ulcerations which represent the precursors in some instances of chronic peptic ulcer

Etiology and Pathogenesis Acute irritation gastritis is caused by (1) dietary indiscretions (excess coffee tea mustard pepper and curry) (2) alcohol abuse (3) thermal influences (hot food) (4) mechanical distention (voracious eating or a sudden excess of food) (5) chemical irritants (salicylates ammonium chloride quinine digitalis)

(6) corrosive agents (acids lye mercuric chloride) or (7) food allergy in rare instances

Aspirin and alcoholic gastritis deserve special consideration because of the frequency with which they occur Alcohol acts both as an irritant and a powerful stimulant of gastric acidity producing an acute gastritis which may develop later into a chronic atrophic form There appears to be a dif ference in individual susceptibility to alcohol In the gastroscopic examination of 100 men consuming an average of 2 8 pt of alcohol daily for 20 years the stomach was found normal in 55 per cent of the men although severe gastritis was observed in the remaining group despite no apparent difference in nutrition or vitamin intake

Aspirin can produce local inflammation and hemorrhage particularly when introduced into an empty stomach In view of the large amount of aspirin ingested each year the observation of hemorrhage or gastritis following aspirin intake may be coincidental or may depend upon the time interval between food intake and aspirin ingestion

Acute infectious gastritis often accompanies acute bacterial and viral diseases particularly acute in fections of childhood *Acute phlegmonous gastritis* a rare pyogenic inflammation of the gastric wall may follow intraabdominal surgery or result from hematogenous spread of streptococci staphylococci or *Escherichia coli* organisms from septic endo carditis infectious diseases or septicemia

Alarming stimuli and emotional disturbances may produce gastritic ulcerations and an erosive gastritis by altering the circulation of the stomach and in creasing gastric secretion Fatigue and emotional lability appear to lower tissue resistance to irritants infections and other exogenous factors rendering the stomach more susceptible to gastritis particu larly in debilitated or malnourished patients

Pathology The acute inflammatory process is characterized by an interstitial cellular infiltration of the stomach wall with lymphocytes plasma cells and polymorphonuclear leukocytes Edema hemor rhage or erosions of the papillae may be observed depending upon the extent and severity of the in flammation Corrosive agents produce a particularly severe inflammatory reaction with necrosis mu cosal hemorrhage and edema A pangastritis with cystic glandular degeneration and superficial ulcera tion often occurs in the acute infectious type Phlegmonous gastritis is associated with abscess formation and diffuse purulent inflammation with necrosis of the gastric wall

Diagnosis The diagnosis of acute gastritis is made with certainty only by the gastroscopic ex amination which permits direct observation of the stomach lining in its finest details The appearance of the engorged mucosa presenting edema excess mucus erosions and hemorrhages is well described by Beaumont during his observations of Alexis St Martin s stomach seen through a fistula

> There are sometimes found on the internal coat of the stomach eruptions or deep red pimples not numer ous but distributed here and there upon the villus membrane rising above the surface of the mucus coat These are at first sharp pointed and red but frequently become filled with white purulent matter At other times irregular circumscribed red patches varying in size or extent from half an inch to an inch and a half in circumference are found on the internal coat These appear to be the effects of congestion in the minute blood vessels of the stomach

The roentgenographic demonstration of thickened rugae constitutes a presumptive diagnosis of gas tritis Superficial ulcerations do not invade the muscularis and therefore cannot be visualized al though they may produce bleeding and pain

Symptoms Acute gastritis is often a self limited disease producing no symptoms In some instances depending upon the intensity and duration of the provocative agent and the individual s susceptibility the patient may complain of epigastric burning fullness anorexia nausea or vomiting A gnawing ulcerlike pain and gastric hemorrhage are common with erosive gastritis particularly after acute alcohol excess prolonged aspirin intake or ingestion of corrosive substances

Morning nausea and vomiting is a prevalent symptom among patients with alcoholic gastritis usually appearing after the first swallow of food or liquid upon arising Aspirin may produce epigastric pain or bleeding in patients with duodenal or gastric ulcer with or without an associated gastritis Perfor ation shock or pyloric obstruction resulting from scar tissue formation are complications of acute cor rosive gastritis Acute phlegmonous gastritis is char acterized by the sudden onset of acute abdominal pain and high fever associated with chills vomit ing and prostration simulating the perforation of peptic ulcer acute cholecystitis or pancreat tis

Treatment Since the disease is usually self limited no specific therapy is indicated other than the removal of irritants or other provocative agents avoidance of dietary indiscretions and the treat ment and prevention of infection An ulcerlike regimen with antacid therapy may be helpful in erosive gastritis In acute corrosive gastritis the proper antidote should be administered as soon as the corrosive agent is removed and further intuba tion avoided because of the danger of perforation and hemorrhage The treatment of acute phleg matous gastritis consists of intensive antibiotic therapy surgical drainage of the localized abscess and in rare instances subtotal gastrectomy The

management of hemorrhage will be discussed in Chap 245

Chronic Gastritis

Chronic gastritis may result from any form of acute gastritis and is caused by (1) chronic irritation (2) dietary indiscretions (3) chronic infections (4) stress and emotional disturbances (5) chronic circulatory disturbances (chronic congestion) (6) deficiency states and (7) prolonged roentgen radiation Other etiologic factors remain to be determined

Roentgenography may suggest the presence of chronic gastritis but the specific diagnosis depends upon the gastroscopic or histologic examination A correlation between the histologic and gastroscopic diagnosis has been documented by Schindler although recent gastric biopsy studies do not establish this relationship consistently Three types of chronic gastritis have been described chronic superficial, atrophic and hypertrophic gastritis

Chronic Superficial Gastritis

This disease comprises approximately 25 per cent of all chronic gastritis and is characterized gastroscopically by (1) hyperemia and reddening of the mucous membrane (2) edema (3) patches of adherent sticky white or whitish gray mucus and (4) mucosal hemorrhages and small erosions

Pathology The histologic abnormalities occur in *the mucosa and submucosa where edema plasma* cells and red cells are observed beneath the surface epithelium Interruptions in the continuity of the mucosa over hemorrhagic areas represent hemorrhagic erosions

Chronic Atrophic Gastritis

This chronic inflammatory disease which constitutes 35 per cent of all chronic gastritis leads to the progressive destruction of the gastric glands

The gastroscopic picture presents (1) a gray or greenish gray color caused by the thinning of the mucosa, as contrasted to the orange red color of the normal stomach and (2) branching blue or purple blood vessels visible through the thin mucosa

Pathology The pathologic picture is characterized by (1) marked thinning of the mucosa, (2) disappearance of the chief and parietal cells of the gastric glands (3) transformation of epithelial cells into goblet cells (4) extensive interstitial infiltration with plasma cells and (5) metaplasia to an intestinal type of epithelium Uncomplicated atrophic gastritis is unaltered histologically by its association with gastric malignancy or pernicious anemia.

Relationship to Pernicious Anemia Polyps and Cancer An atrophic mucous membrane is invariably present at autopsy in pernicious anemia and occurs in a high percentage of patients with gastric polyps and gastric cancer There is considerable evidence that the atrophic mucosa is the precursor of these diseases Adenomatous polyps were found in 7 to 14 per cent of a series of 878 collected cases of pernicious anemia studied by roentgenography gastroscopy or autopsy (Table 123) Carcinoma of the stomach occurred in 4 to 12 per cent of this series and was observed three to eight times more frequently than in a control group of the same age

Chronic Hypertrophic Gastritis

This form of gastritis is characterized by hyperplasia and thickening of the gastric mucosa a tendency towards tumefaction hemorrhage and ulcer like symptoms It comprises 40 per cent of all chronic gastritis

Table 123 INCIDENCE OF ATROPHIC GASTRITIS ADENOMATOUS POLYPS AND CARCINOMA OF THE STOMACH IN PERNICIOUS ANEMIA

Investigators	Total cases of pernicious anemia examined	Polyps	Carcinoma	Atrophic gastritis	Method of study
Brown	151	12 (8%)		151 (100%)	Autopsy
Hardt Schwartz Steigmann	100	7 (7%)	4 (4%)	59 (59%)	Gastroscopy
Kaplan and Rigler	293		36 (12 3%)		Autopsy
Rigler and Kaplan	211	15 (7 1%)	17 (8 0%)		X ray
Schindler	43	6 (14%)		43 (100%)	Gastroscopy
Young Loefenstein Cray	80	8 (10%)	4 (5 0%)	[illegible]	Gastroscopy

The gastroscopic appearance is that of a velvety cobblestone mucosa with diffuse granular nodularity Sometimes these polypoid excrescences may be difficult to distinguish from true polyps or tumor infiltration Erosions or small ulcerations are common

Pathology Hypertrophic gastritis may occur as (1) hypertrophic interstitial gastritis with dense lymphocytic and plasma cell infiltration and (2) hypertrophic proliferative gastritis in which there is a marked proliferation of the surface epithelium forming irregular nodes A tremendous overgrowth of the glandular apparatus may treble the thickness of the mucosa in some instances simulating a neoplasm

Postoperative Gastritis

Severe hypertrophic or erosive gastritis may occur following gastric resection or gastroenterostomy for peptic ulcer The gastritis is often localized to the site of the anastomosis or may involve the entire stomach Postoperative gastric distress or hemorrhage may result The treatment is the same as that of recurrent ulcer

Symptoms of Chronic Gastritis Chronic gastritis is often asymptomatic Ulcerlike distress may occur with superficial and hypertrophic gastritis particularly if erosions are present The pain differs usually from that of true peptic ulcer in its time relationship and persistence after food Anorexia and epigastric burning are not uncommon Gastric acidity is usually increased in hypertrophic gastritis and is absent in one third of the patients with atrophic gastritis

Massive hemorrhage is a frequent complication of hypertrophic gastritis and is seen in atrophic gastritis when a submucosal vessel is eroded Gastritis bleeding plays a significant role in massive hemorrhage of undetermined origin since the source may not be identified roentgenographically

Course and Prognosis Chronic superficial gastritis is usually self limited and heals rapidly Occasionally it develops into atrophic gastritis The atrophic form remains unchanged in spite of liver or vitamin therapy and deserves repeated examination because of the increased incidence of gastric cancer Hypertrophic gastritis has little tendency to heal and usually persists in spite of treatment

Treatment There is no specific treatment An ulcer regimen including a bland diet and antacids may relieve the distress when ulcerations are present Liver extract and vitamins have been reported to reverse the gastroscopic appearance of atrophic gastritis but there is no evidence that the histologic or clinical picture is improved

GASTRIC ULCER

Benign gastric ulcer will be discussed in Chap 245

TUMORS OF THE STOMACH

Benign Tumors of the Stomach

Definition Benign gastric tumors may be of epithelial or connective tissue origin The epithelial tumors consist of adenomatous polyps adenomas and papillomas The connective tissue tumors include (1) smooth muscle tumors (leiomyomas fibromyomas myomas and adenomyomas) (2) neurogenic tumors (neurilemmomas and neurofibromas) (3) lipoma (4) angioma (hemangiomas and lymphangiomas) (5) dermoid cysts and (6) myxomas osteomas chondromas and lymphomas A rare benign tumor of the stomach is caused by proliferation of aberrant pancreatic tissue

Gastric Polyps

Pathology Adenomatous polyps the most common of all epithelial tumors appear most frequently in the pyloric region of the stomach The benign gastric polyp is usually an adenoma although the term *polyp* refers to its gross rather than its histologic structure Adenomas are composed of epithelial tubules with a connective tissue stroma which rarely breaks through the muscularis mucosa and they appear as sessile or pedunculated tumors loosely attached to the mucous membrane by a pedicle of varying length Solitary adenomas occur in one half the cases

Menetrier introduced the term *polyadenomes polypeux* in 1888 to describe multiple adenomas of the stomach (*diffuse polyposis*) consisting of innumerable discrete lobulated pedunculated often cystic tumors each with its own independent attachment to the stomach mucosa The disease usually is seen in the antrum although the whole stomach may be involved In rare instances polyposis of the colon occurs concomitantly (Fig 171)

The most important aspect of the adenomatous polyp particularly of the large polyp associated with anacidity is its tendency to malignant change The relationship of polyp formation to gastric anacidity atrophic gastritis pernicious anemia and carcinoma is discussed elsewhere (Table 123)

Another form of polyposis called *polyadénomes en nappe* presents a thickened plaquelike base characterized by closely packed flat projections from the mucous membrane without pedicles or cystic changes They are not true adenomas but represent simple hypertrophy or hyperplasia of the gastric mucosa grafted upon a severe hypertrophic gastritis These lesions do not undergo malignant

change and are often described as *giant hypertrophy of the gastric rugae* or *giant hypertrophic gastritis*

Connective Tissue Tumors

Smooth muscle tumors occur most commonly near the pylorus as either solitary or multiple neoplasms They usually project into the stomach lumen as pedunculated intragastric tumors but may involve the subserous coat growing within the confines of the gastric wall or extending outside the stomach Neurogenic tumors are most commonly found on the lesser curvature near the pylorus and angiomas usually occur in the body and antrum of the stomach

Symptoms of Benign Tumors Benign tumors of the stomach produce no symptoms unless they obstruct the pylorus ulcerate or bleed A polyp may prolapse through the pylorus and occasionally cause obstruction The most consistent symptom is anemia resulting from continuous bleeding This may take the form of massive hemorrhage or continuous oozing Usually the anemia is of the hypochromic iron deficiency type but macrocytic anemia may occur with gastric polyps Large mesenchymal tumors may present an abdominal mass or they may ulcerate producing postprandial discomfort suggestive of peptic ulcer

Diagnosis Adenomatous polyps are diagnosed by gastroscopic examination or the roentgen demonstration of a round discrete movable filling defect in a pliable stomach wall Histamine anacidity is commonly associated

Mesenchymal tumors occur at any age but the diagnosis is suggested by its appearance in the younger age group Demonstration of a circumscribed intramural mass suggests a connective tissue tumor Gastroscopically the tumor appears to lie beneath an intact mucosa and moves with the wall of the stomach during peristaltic activity When a benign tumor ulcerates differentiation from a malignant lesion becomes more difficult

Treatment All benign neoplasms of the stomach should be removed surgically The possibility of malignant change exceeds the operative mortality risk Operation is often required because of hematemesis melena severe anemia or symptoms of obstruction at the pylorus or antrum Subtotal gastric resection is the operation of choice although in some instances *a small polyp may be excised* locally Simple excision however has been followed in a number of instances by the occurrence of a malignant lesion at the site of the original growth Total gastrectomy may be necessary in cases of diffuse polyposis and multiple benign tumors Prognosis following adequate removal of the benign gastric neoplasm is excellent.



FIG 171 Multiple polyps of the stomach The classical picture of *polyadenomes polypeux* in a 53-year-old woman with a history of hematemesis Total gastrectomy was performed, and the stomach revealed 35 to 40 benign polyps each with a discrete stalk.

Carcinoma of the Stomach

Cancer of the stomach ranks high among the common causes of death It is responsible for approximately 25 000 deaths in the United States annually and 10 per cent of all cancer deaths Although it may occur in patients under twenty years of age and is not uncommon from thirty five to fifty the incidence increases with maturity and is highest between the ages of fifty and sixty nine with a male preponderance The disease is encountered among all races in all parts of the world.

Etiology The cause of gastric cancer is unknown *There is no conclusive proof that alcohol hot foods* or superheated fats are carcinogenic in human beings The incidence of gastric cancer is unrelated to trauma, occupation or dietary indiscretion. Although susceptibility to gastric cancer appears to be inherited in some families it is doubtful that heredity is a primary factor Filtrable viruses and various carcinogens such as methylcholanthrene are

under investigation The concept of benign gastric ulcer as a precancerous lesion which has not been universally accepted will be discussed in Chap 245

Significance of Atrophic Gastritis in Gastric Cancer The relationship of gastric polyps and cancer to an atrophic gastric mucous membrane has been referred to in the discussion of atrophic gastritis (Table 123) The demonstration of the transitional stages from chronic atrophic gastritis with small areas of regenerative hyperplasia to papilloma and finally to carcinoma led Konjetzny and other investigators to consider the atrophic mucosa as a precancerous lesion offering fertile soil for the growth of gastric cancer

In the authors series of 80 pernicious anemia patients four cancers (5 per cent) and eight polyps (10 per cent) were observed all occurring in the antrum of stomachs with atrophic gastritis (Table 123) It does not follow that every atrophic membrane will undergo malignant change or that all cancers arise on the basis of a chronic atrophy Although gastric cancer may appear in an essentially normal gastric mucosa the probability of developing cancer is three times greater in patients with chronic atrophy than in the average normal adult in the same age group

Pathology Approximately 50 per cent of all gastric cancers occur in the antrum or pyloric canal and 25 per cent involve the lesser curvature The cardia and greater curvature are each involved in approximately 8 per cent the remaining 9 per cent of tumors occurring on the anterior and posterior walls of the body of the stomach Cancers of the cardia or pylorus often produce symptoms before the tumor achieves any great size but lymphatic invasion to the regional nodes occurs comparatively early Cancer involving the pyloric canal or adjacent antrum may be the most malignant metastasizing early before the growth has achieved any remarkable size In general however the site of the growth does not significantly alter the prognosis although it may influence early diagnosis Large primary tumors often metastasize less rapidly than small neoplasms

Grossly the tumor appears as (1) a polypoid mushroomlike sharply circumscribed growth protruding into the lumen of the stomach (2) an ulcerating cancer or (3) a diffusely infiltrating lesion

Cancer of the stomach may exist as a simple adenocarcinoma or as a papillary colloid gelatinous medullary or scirrhous carcinoma The *circumscribed* scirrhous carcinoma often produces the common type of ulcerating cancer which may simulate benign gastric ulcer Histologically the tumor presents an excess of fibrous tissue with cancer cells appearing between the strands of connecting tissue Early invasion of the regional lymph nodes is common The *diffuse* scirrhous carcinoma transforms the stomach into a rigid shrunken thick walled inflexible structure—the so called leather bottle stomach or *linitis plastica*

The malignancy of tumors may be classified on the basis of degree of differentiation microscopically (Broders classification) The well differentiated tumors metastasize least rapidly and present the best prognosis whereas the poorly differentiated tumors tend to metastasize early

Gastric cancer spreads by direct extension or infiltration to the pancreas liver colon gallbladder esophagus spleen or diaphragm and least often to the duodenum Metastasis takes place by way of the lymphatics peritoneum or blood stream The regional lymph nodes are the first to be involved The next most common sites are the omentum peritoneum and liver followed by the left supraclavicular lymph nodes rectum ovaries lungs bones adrenal glands and brain approximately in that order Metastases to the navel skin and bone marrow are rare

The left supraclavicular node (Ewalds node Virchows node sentinel node) is involved in approximately 5 per cent of cases of gastric cancer at autopsy This involvement appears late in the disease The so called *Krukenberg tumor* may occur in an equal number of cases as a result of peritoneal spread invariably involving both ovaries Metastases in the rectal pouch of the male may present themselves as the *rectal shelf of Blumer*

Symptoms The onset of carcinoma of the stomach is so insidious that an estimated 50 per cent of all gastric cancers extend beyond the stomach before the first symptoms appear and 12 to 18 months usually elapse before the diagnosis is made Symptoms are frequently completely absent or very indefinite in nature until the growth has attained sufficient size to produce ulceration bleeding obstruction or secondary infection Alertness on the part of the physician to the early diagnosis of gastric cancer offers the only hope at present to more successful therapy

Anorexia vague epigastric discomfort slight nausea after meals and weight loss of 10 to 15 lb are among the first signs of gastric cancer Nausea and vomiting associated with fullness after meals may indicate beginning pyloric obstruction or interference with gastric motility and distensibility Intractable vomiting of food and gastric juice may be an early symptom of small tumors invading the pyloric canal although it usually occurs late in the disease The vomitus contains food bile or blood presenting a "coffee grounds" appearance resulting from the prolonged action of hydrochloric acid

Epigastric distress if present is exceedingly variable It may consist of vague discomfort in the epi

gastrium a sensation of fullness burning or a very mild cramping distress occurring after a heavy meal or minor dietary indiscretion A true ulcerlike syndrome may be the principal complaint particularly if the ulceration is associated with acid gastric juice or if the lesion is located in the distal portion of the stomach interfering with normal tone and motility In some instances it cannot be distinguished from true ulcer distress but usually the *relief of pain after foods or antacids is incomplete* and the pain occurs shortly after meals and before breakfast

Hematemesis and melena may be the presenting symptoms or may not occur until late in the disease *Anemia is often but not invariably present*

Occasionally perforation of an ulcerating cancer or a septic fever (suggesting abscess or metastases to the liver) may be the first clinical manifestation Low grade fever is not uncommon with gastric cancer Carcinoma of the cardiac portion of the stomach simulates diseases of the lower esophagus and may produce vague substernal distress or slight dysphagia *following solid food intake*

Physical Examination In the early stages there are no discernible abnormalities As the disease progresses weight loss pallor a palpable movable hard mass in the upper abdomen or nodular enlargement of the liver may become evident A firm hard node in the left supraclavicular area (Ewald s node Virchow s node or sentinel node) is a late and infrequent finding Metastases to both ovaries (Krukenberg s tumor) are likewise uncommon Metastatic involvement of the prerectal cul-de sac presents a hard shelflike projection or mass above the prostate or in a similar position in the female (*rectal or Blumer s shelf*) Normal soft velvety rectal mucosa can be palpated overlying the neoplasm distinguishing it from an intrarectal growth

Laboratory Examination There is no free hydrochloric acid in the gastric juice after histamine stimulation in approximately 60 to 70 per cent of patients with gastric cancer In the presence of an ulcerating gastric lesion persistent anacidity is highly suggestive of malignancy since free acid is usually demonstrable with a benign gastric ulcer Normal or increased gastric acidity however does not exclude the diagnosis of cancer Occult blood in the gastric contents or the stools is found in a large percentage of cases at some time during the course of the disease The stools may be consistently negative however in the presence of an *extensive cancer of the stomach The blood count* is often normal or discloses a normocytic or hypochromic microcytic anemia particularly if there is chronic blood loss Direct suppression of the bone marrow can produce definite anemia in the absence of blood loss Characteristic malignant cell nuclei may be found upon staining the gastric sediment by Papanicolaou s method particularly with a more cellular type of lesion or following the use of an abrasive balloon or gastric lavage with papain or chymotrypsin

Plasma and Urinary Pepsinogen in Gastric Cancer The plasma and urinary pepsinogen (uropepsin) *reflect the peptic activity of the stomach* Plasma pepsinogen is derived from the secretion of pepsinogen directly into the blood stream by the peptic cells Pepsinogen is then transported to the kidneys and excreted in the urine as uropepsin The uropepsin excretion usually exceeds 1 000 units in normal individuals and in patients with duodenal or benign gastric ulcers In the presence of a gastric lesion a very low uropepsin excretion suggests malignancy (Table 124) although a normal excretion does not exclude it A low plasma pepsinogen in the presence of gastric ulceration is also a strong indication of cancer

Roentgenologic Examination *The roentgenologic* examination is the most reliable method for detecting gastric cancer Careful fluoroscopic study and repeated examinations yield an accurate diagnosis in approximately 90 per cent of cases

The most common roentgen evidence of gastric cancer is the "filling defect which appears as a

Table 124 UROPEPSIN EXCRETION IN PEPTIC ULCER GASTRIC CANCER AND PERNICIOUS ANEMIA

Condition	Patients	Average uropepsin excretion units/24 hr	Uropepsin excretion units/24 hr percentage		
			0–1 000	1 000–3 000	3 000+
Normal	265	3 670	2 6	52 7	44 7
Duodenal ulcer	205	8 471	0	0	100
Gastric ulcer	90	5 756	1 1	19 3	79 6
Gastric cancer	73	1 939	57 5	19 2	23 3
Pernicious anemia (atrophic gastritis)	80	13	100	0	0

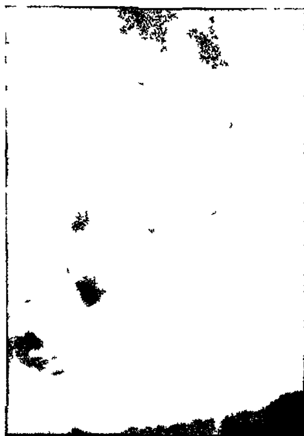


Fig 172 Ulcerating colloid adenocarcinoma of the lesser curvature The crater is surrounded by an irregular halo produced by the thickened infiltrated wall surrounding the ulcer The patient presented profound anemia and metastases to the lymph nodes and bone marrow

constant often rigid space occupying lesion subtracting from the normal outline of the stomach A polypoid tumor growing into the lumen appears as an opaque often nodular mass when pressure is exerted over the barium filled area

An ulcer appears as a collection of barium in a crater or niche It is considered malignant when associated with a space occupying deformity or filling defect Ulcers on the greater curvature of the stomach have a high incidence of malignancy An ulcer with a thickened raised wall appears as a crater (or a collection of barium) surrounded by a translucent halo the meniscus sign of Carman which suggests malignancy particularly if observed beneath the line of the lesser curvature (Fig 172)

The scirrhous type of cancer produces a constant rigid often ragged alteration in the contour of the stomach with destruction or distortion of the mucosal pattern (Fig 173) Both curvatures of the antrum may be involved producing a stiff annular defect surrounding a narrowed lumen (Fig 174) The diffuse scirrhous carcinoma may give rise to a typical small contracted stomach referred to as the leather bottle stomach described previously

Approximately one fifth of all gastric cancers present clinical and roentgen evidence of obstruction When there is complete obstruction it may be impossible for the roentgenologist to distinguish a pyloric cancer from a duodenal ulcer with high grade stenosis Obstruction from cancer is more likely to be complete and the contour of the obstructed area is often more ragged as a result of infiltration

Malignant lesions of the cardia of the stomach which have not invaded the lower esophagus or the lesser curvature may be overlooked by roentgen examination Examination by esophagoscopy gastroscopy and the double contrast technique with air and barium are helpful in the detection of lesions in this area

Gastroscopic Examination Gastroscopic examination of the stomach complements the roentgen examination and should always be preceded by it The maximum diagnostic accuracy is obtained by employing both methods since either alone may fail to demonstrate a lesion If the roentgenographic findings are conclusive however gastroscopy is *not essential* The procedure is *often helpful in* evaluating questionable roentgen defects or con



Fig 173 Undifferentiated adenocarcinoma of the lesser curvature of the stomach in a 29 year old man with metastases to the liver and supraclavicular nodes

firming the diagnosis of cancer and determining the type extent and operability of the tumor Gastroscopy may be employed to help differentiate benign from malignant lesions and intragastric from extragastric tumors Cancers on the posterior wall of the fundus or at the cardia which are often difficult to visualize roentgenologically may be seen gastroscopically in some instances

Polypoid malignancies are readily recognized since they protrude into the lumen although the differentiation from benign tumors or hyperplastic forms of gastritis is difficult.

A negative gastroscopic examination does not exclude the diagnosis of cancer associated with lesions in the "blind areas" of the stomach

The interpretation of the gastroscopic picture is dependent largely upon the skill and experience of the endoscopist Infiltrating carcinomas are difficult to distinguish gastroscopically from lymphoma and diffuse hypertrophic gastritis Gastric biopsy in these instances may be helpful

An ulcerating carcinoma is characterized by (1) nodularity or stiffness of the wall (2) blending of the borders of the ulcer which lack the cleanly cut sharply punched-out appearance of the benign lesion and (3) stiffness nodularity or infiltration throughout the area

Early Diagnosis and Screening Procedures Approximately 75 per cent of all patients with gastric cancer who come to operation cannot be cured because of lymph node metastases Since the symptoms of early cancer of the stomach are absent vague or indefinite necessitating a period of 12 to 18 months for recognition early diagnosis and treatment are of prime importance

Earlier diagnosis may be achieved by (1) repeated roentgenographic and gastroscopic examinations in all patients in middle life who develop indigestion or abdominal distress (2) viewing all gastric ulcers with suspicion until they are healed completely according to roentgenographic and gastroscopic examination (3) removing gastric polyps as soon as they are found particularly if there is an associated histamine anacidity and (4) subjecting patients with pernicious anemia and chronic atrophy of the stomach to repeated roentgen and gastroscopic examinations at regular intervals

Further advances in early diagnosis may be forthcoming from cancer prevention clinics and screening procedures such as routine photofluorography of the stomach and the newer techniques of exfoliative cytology for the early demonstration of cancer cells Increased accuracy of cytologic diagnosis has been made possible by gastric lavage with papain or with chymotrypsin and the use of abrasive balloons The technical complexities of this cytologic technique prevent its wide use as a screening procedure although selected screening is feasible



Fig 174 Annular adenocarcinoma of the stomach involving the antrum producing a narrowed lumen in a 60 year-old male with a 10-year history of pernicious anemia

particularly in differentiating benign from malignant gastric ulcer The use of gastroscopic biopsy may also help in correlating tissue morphology with the cell type seen in the cytologic preparation

Other screening procedures include (1) examination of the stools for occult blood by the benzidine dihydrochloride method (2) the determination of free gastric hydrochloric acid by a urinary method using the quininium or azure A exchange indicator compounds and (3) the measurement of the uropepsin excretion in the urine discussed previously

Differential Diagnosis An ulcerating cancer of the stomach may simulate a benign gastric ulcer particularly in the early phase of the disease The methods of distinguishing benign from malignant ulcers of the stomach by clinical laboratory roentgenologic and gastroscopic criteria are discussed in Chap 245

Complications The complications of gastric cancer are (1) perforation into adjacent organs (2) hemorrhage (3) obstruction (4) metastatic involvement to other parts of the body Acute perforation is rare Chronic perforation into the pancreas and less frequently into the duodenum jejunum or colon occurs late in the disease and may be recognized clinically by the onset of severe pain or the presence of a palpable mass produced by the inflammatory reaction

While oozing and minor bleeding from gastric carcinoma are common as evidenced by the presence of occult blood in the stools or the coffee grounds appearance of the vomitus massive hemorrhage occurs less frequently in cancer than in benign peptic ulcer

Obstruction from lesions invading the pylorus or cardiac orifice of the stomach may cause pain nausea and vomiting or dysphagia Constricting *lesions in the middle of the stomach* producing the so called *hourglass stomach* rarely cause obstruction

Prognosis and Mortality Rate Lymph node metastases are demonstrable in 65 to 75 per cent of patients who come to operation In this group the 5 year survival rate when gastric resection is possible is only 5 to 10 per cent Of the remaining 25 to 35 per cent of patients who are operated on for gastric cancer with no demonstrable lymph node involvement the survival rate is approximately 35 per cent The survival rate for all patients with gastric cancer probably does not exceed 12 per cent although statistics for the country as a whole would indicate that 5 to 8 per cent of all persons coming to a clinic or hospital with gastric cancer survive 5 years or more This figure includes patients who are frankly inoperable as well as those who are submitted to palliative operative procedures The prognosis is not affected significantly by sex or age although carcinoma may spread more rapidly in the young

The immediate surgical mortality rate depends upon the individual s surgeon s criteria for resectability A high mortality rate above 10 per cent may indicate that too many resections are being attempted while the mortality rate of 5 per cent or less may indicate too few Recent mortality rates approximate 8 per cent for subtotal resection and 13 per cent for total resection for gastric cancer The only hope for this disease at the present time is early diagnosis and a reasonably heroic surgical approach

Treatment All ulcerating lesions of the stomach should be viewed with considerable suspicion until they prove to be benign When a gastric ulcer appears benign by roentgen and gastroscopic examination a trial of medical ulcer management with antacids and antispasmodics is justified for a period of 4 to 8 weeks if free gastric acidity can be demonstrated and the cytologic examination of the gastric contents is negative If the lesion does not heal completely by roentgen and gastroscopic examination after 4 to 8 weeks of good medical management or if abdominal pain or occult blood in the stools persists and there is reasonable doubt of the diagnosis of benignity then surgical exploration is indicated (The differential diagnosis and treatment of gastric ulcer is discussed in Chap 245)

The ideal treatment for the early lesion of gastric cancer is complete surgical removal by subtotal gastric resection The more advanced gastric cancer regardless of the gross or histologic appearance also should be removed if possible by subtotal or total gastric resection Total gastrectomy for lesions diffusely infiltrating the stomach wall with *excision of the entire lymphatic drainage area* is now being recommended since life may be prolonged by the procedure in spite of the lymphatic involvement The simultaneous removal of a gastric cancer and metastatic lesions elsewhere such as ovarian implantations may prove beneficial Although metastases to the peritoneum bone marrow and liver are considered relative contraindications to resection a subtotal palliative resection in selected cases is often indicated particularly when the tumor threatens obstruction If the tumor cannot be resected a gastroenterostomy is unlikely to be helpful

Medical management consists of symptomatic supportive and psychologic treatment of the patient A soft bland high caloric palatable diet as unrestricted as possible is prescribed as tolerated The diet is supplemented with iron and vitamins Narcotics may be used freely but discriminately along with sedatives hypnotics and analgesics The parenteral administration of fluid and electrolytes and occasional blood transfusions are helpful as supportive measures A bland ulcer type of diet with frequent feedings antacids and antispasmodics may afford symptomatic relief to patients with ulcerating cancers particularly those with free acid in the gastric juice

There is no satisfactory proof that roentgen therapy is of value in the treatment of gastric cancer although it is effective in the treatment of lymphoblastoma and malignant mesenchymal tumors of the stomach The nausea vomiting and anorexia induced by intensive radiation therapy contraindicate its use in gastric carcinoma The therapeutic value of high voltage deeply filtered therapy which may be applied directly to the tumor without injury to other tissues remains to be determined

Psychologic Approach to the Patient As a general principle it is advisable to withhold the diagnosis of gastric cancer from the patient but it should be freely and openly discussed with the next of kin or a responsible member of the family particularly from the viewpoint of diagnosis and treatment Most patients eventually know they have cancer but cling to the ray of hope that they may be mistaken This reasonable doubt regarding the diagnosis exerts a sustaining influence in their atti

tude to the disease The patient may repeatedly interrogate the physician and urge him outwardly to reveal the diagnosis hoping fervently that the true facts will not be divulged Cautious optimism on the part of the physician is necessary in the day to-day handling of the problems which arise

Above all the physician must encourage and sustain the patient with a positive hopeful optimistic approach New drugs and treatments offer new hope In selected instances oral cortisone in doses of 100 to 150 mg daily may be exceedingly (although temporarily) helpful in increasing the patient s appetite producing a state of euphoria and sustaining the patient psychologically during the terminal period It does not of course alter the course of the disease If used judiciously in the absence of electrolyte imbalance or marked vomiting cortisone may be a blessing to the patient and the family during the last trying days

Malignant Tumors of the Stomach Other Than Carcinoma

Definition This group of tumors includes sarcoma lymphosarcoma reticulum cell sarcoma Hodgkin s disease and lymphoblastoma Sarcomas constitute 1 to 4 per cent of all tumors of the stomach Among the sarcomas the reticulum cell sarcoma (31 per cent) and leiomyosarcoma (27 per cent) are the most common Lymphosarcoma (23 per cent) Hodgkin s disease (15 per cent) and lymphoblastoma (4 per cent) complete the list

Symptoms The age of onset of sarcoma is approximately 10 years younger than that of carcinoma The most prominent symptoms are pain loss of weight and a palpable mass Splenomegaly occurs in 10 per cent of gastric sarcoma Massive bleeding is a common complication particularly with leiomyosarcoma Obstruction and perforation are rare

Sarcomas may invade the blood stream more often than carcinoma although lymphatic permeation and metastases are seen more often with carcinoma The neurogenic sarcoma lymphosarcoma and fibrosarcoma metastasize late in the course of the disease although the round cell tumors and the myosarcomas are much more malignant growing rapidly and metastasizing early

Enlargement of the superficial glands occurs with lymphosarcoma and Hodgkin s disease Anemia splenomegaly fever an abdominal mass and lymphadenopathy suggest the diagnosis of Hodgkin s disease

Diagnosis The roentgen appearance of sarcoma may simulate that of carcinoma The differential between the two is difficult and often depends upon the histologic examination In some instances gastric biopsy has been helpful and exfoliative cytology may be useful Biopsy of large glands from the cervical region is often indicated Gastroscopically the differential between carcinoma sarcoma and leukemia or Hodgkin s disease is exceedingly difficult

Treatment These tumors in general are considerably more radiosensitive than carcinoma Gastric resection followed by roentgen therapy is advocated Lymphosarcoma is more responsive to deep radiation therapy than any other type of gastric tumor particularly the small round cell lymphosarcoma Good results from roentgen therapy have also been reported in Hodgkin s disease of the stomach

DISEASES SIMULATING GASTRIC MALIGNANCY

A number of disease processes are characterized by diffuse inflammatory reaction and ulceration which resemble malignant infiltration and present difficulties in clinical and roentgen diagnosis

Giant Rugal Hypertrophy Occasionally giant enlargement of the mucosal folds presents the appearance of neoplasm both roentgenologically and gastroscopically A combination of hypertrophy and hyperplasia may appear as *polyadenomes en nappe* sometimes called *giant hypertrophy of the gastric rugae* or *giant hypertrophic gastritis* Gastric biopsy and exfoliate cytology may be helpful in diagnosis but gastric resection is often necessary because of the difficulty in distinguishing this disease from cancer or lymphoma (Fig 175)

Linitis Plastica *Linitis plastica* is a term selected by Lewis Brinton in 1854 to describe an excessive connective tissue response to malignancy or infection of the stomach This disease is characterized by a diffuse fibrosis of the gastric wall associated with shrinkage thickening and a diminished capacity It is sometimes called *leather bottle stomach* or *cirrhosis of the stomach* The principal pathologic finding is extensive connective tissue proliferation in the submucosa The disease is most common in males between the ages of forty and seventy

Etiology The principal causes are (1) diffuse scirrhous carcinoma or occasionally gastric sarcoma Hodgkin s disease or leukemia (2) gastric syphilis (3) phlegmonous gastritis

Symptoms The initial complaint is that of a feeling of fullness after a small meal accompanied by regurgitation and vomiting A progressive decrease in gastric capacity results in marked weight loss and anemia Hematemesis perforation and obstruction are rare

Diagnosis Roentgenograms present a smooth rigid contracted stomach with diminished peristalsis



FIG 175 Giant rugal hypertrophy presenting the appearance of a neoplasm in a 47 year old man with melena Microscopic examination revealed a thickened mucosa with elongated cystically dilated gastric glands There was no evidence of malignancy

and rapid evacuation of the barium The gastroscopic appearance is that of diffuse infiltration and stiffness of the mucosa A mass may be palpated in some instances Achlorhydria occurs in approximately 75 per cent of cases

Treatment Linitis plastica must be regarded as a malignant lesion unless proved otherwise The surgical treatment is that of gastrectomy frequently *total gastrectomy If the Wassermann test is positive* surgery should be deferred until the patient has been given antisyphilitic therapy

Syphilis of the Stomach The characteristic lesion of this rare disease is the gumma It may appear as a solitary lesion with ulceration simulating a benign gastric ulcer or as a chronic inflammatory reaction with fibrosis and nodular induration simulating a carcinoma The histologic picture is characterized by perivascular round cell infiltration gummas and obliterating endarteritis

Epigastric ulcerlike pain vomiting gastric hemorrhage and weight loss may occur A mass is rarely palpable Differentiation from cancer may be impossible without a histologic examination The roentgen examination may demonstrate (1) an infiltrative lesion in the prepyloric area (2) constriction of the middle of the stomach resulting in an hour glass deformity (3) diffuse involvement presenting the picture of a linitis plastica The Wassermann test on blood or spinal fluid is frequently positive

Syphilitic lesions of the stomach respond dramatically to antisyphilitic therapy

Tuberculosis of the Stomach Tuberculosis of the stomach is a rare disease encountered more frequently in adults than in children Three types are usually seen ulcerative miliary and granulomatous The ulcerating type is the most common form Clinically it may be impossible to differentiate tuberculosis of the stomach from benign ulcer syphilis or cancer In the vast majority of patients tuberculosis exists elsewhere in the body particularly in the lungs The diagnosis is established by microscopic examination of the lesion removed at laparotomy or by the demonstration of tubercle bacilli

Congenital Hypertrophic Stenosis in Adults The adult form similar to the disease seen in infants consists of a marked hypertrophy and thickening of the pyloric circular muscle

Etiology The cause of this syndrome is unknown In some instances it represents a residual low grade congenital pyloric stenosis producing periodic episodes of nausea and vomiting which can be traced back to infancy When the symptoms begin in adult life however the disease is often associated with a gastric ulcer or gastritis

Symptoms The clinical picture is indistinguishable from that of carcinoma gastritis or peptic ulcer with obstruction The predominant complaints are nausea and vomiting associated at times with vague atypical ulcer distress

Diagnosis Roentgen examination reveals a crescentic indentation of the base of the duodenal bulb produced by the markedly thickened pylorus This appearance frequently cannot be distinguished from that of hypertrophic gastritis an inflammatory reaction surrounding a pyloric ulcer or a scirrhous carcinoma *beginning in the pyloric end of the* antrum

Treatment Treatment may be unnecessary If a gastric ulcer is present the usual ulcer regimen is recommended Surgery should be considered when (1) histamine anacidity is present (2) there is no improvement in the emptying function after 2 to 3 weeks of medical management or (3) there is a reasonable doubt as to the nature of the lesion Subtotal gastrectomy may be necessary since it is as difficult to distinguish a benign from malignant involvement of the pylorus at the operating table as it is preoperatively

CONGENITAL ANOMALIES OF THE STOMACH

Congenital Hypertrophic Pyloric Stenosis of Infancy This disease is characterized by (1) hypertrophy of the pyloric muscle particularly the circular muscle layer and (2) spasm resulting in nar

rowing of the pyloric channel There is no histologic evidence of inflammation Males are affected four times as commonly as females

Symptoms Regurgitation and periodic vomiting herald the onset usually from 2 to 3 weeks after birth to 2 to 4 months The vomiting is often projectile without retching and is followed by rapid weight loss constipation and dehydration A milder clinical form may be seen if spasm predominates

Diagnosis Physical examination reveals visible hyperperistalsis dehydration and malnutrition A small mass the size of a marble or pea may be felt at the right rectus border beneath the costal margin In the milder form the hyperperistalsis and mass may not be evident Enlargement of the stomach and delayed gastric emptying confirm the diagnosis roentgenologically

Treatment An initial trial of medical management with frequent small feedings antispasmodics and correction of electrolyte and fluid imbalance is indicated If conservative treatment fails the Ramstedt operation consisting of a longitudinal incision through the pyloric muscle to the mucosa is recommended and is a uniformly successful procedure

Diverticula of the Stomach *Definition* A diverticulum is an abnormal outpouching or protrusion of the stomach wall forming a permanent sac True diverticula contain all the muscular coats within the wall of the pouch and are usually congenital False diverticula lack the muscular coats and are acquired as the result of pulsion or traction

Incidence Both congenital and acquired gastric diverticula are most often seen in middle aged women The posterior wall of the cardia near the lesser curvature is the most common site for the congenital type Acquired gastric traction diverticula are found most often near the pylorus and are caused by inflammatory or malignant involvement of adjacent organs Bezoars or trauma may produce pulsions diverticula

Duodenal diverticula are more common than gastric The congenital form is seen in the second and third portions of the duodenum Diverticula in the first part of the duodenum usually result from traction produced by a duodenal ulcer

Symptoms Diverticula rarely cause symptoms unless they become inflamed ulcerated or obstructed Associated diseases rather than diverticula may cause epigastric pain vomiting or bleeding

Diagnosis The diverticulum appears by roentgen examination as a barium containing sac projecting from the normal contour of the stomach or duodenum

Treatment Treatment is rarely necessary In selected cases excision or invagination of the diverticulum is indicated

MISCELLANEOUS DISEASES OF THE STOMACH

Prolapse of the Gastric Mucosa *Prolapse of the gastric mucosa* is a phrase used to describe the herniation of a portion of gastric mucosa through the pylorus resulting in a characteristic roentgen appearance It may occur at any age but is usually seen in the fifth decade occurring in 2 to 14 per cent of patients subjected to examination

Etiology The cause is unknown Herniation may be initiated by hyperperistalsis associated with antral gastritis duodenal ulcer or local spasm Excessive mobility of the mucosa upon the muscularis is a contributing factor as is submucosal edema from hypoproteinemia or cardiac failure

Symptoms Prolapse of the gastric mucosa usually produces no symptoms and is discovered as an incidental finding The symptoms attributed to this condition are nonspecific and are probably caused by the accompanying gastritis peptic ulcer or spasm Epigastric distress nausea vomiting weakness weight loss and bleeding have been described

Diagnosis The diagnosis of prolapse is suggested by the roentgen demonstration of (1) an "umbrella or mushroomlike defect in the base of the duodenal bulb and (2) rugae extending through the pylorus into the duodenal cap Gastroscopy usually reveals evidence of chronic hypertrophic gastritis

Treatment If symptoms are present a bland diet with antispasmodics may be prescribed Surgery (subtotal gastric resection) is rarely necessary

Foreign Bodies in the Stomach A wide variety of foreign bodies may be found in the stomach Small objects such as coins and marbles accidentally swallowed by children rarely cause symptoms and eventually pass through the gastrointestinal tract Sharp pointed objects (pins needles) may penetrate the wall of the stomach or intestine producing peritonitis or an abscess Large foreign bodies (spoons knives forks) found in the stomachs of the insane usually produce no symptoms although ulceration perforation or obstruction may occur

Bezoars are conglomerations of swallowed foreign material consisting of hair (trichobezoar) hair and vegetable fiber (trichophytobezoar) or of vegetable fiber alone (phytobezoar) The prolonged use of calcium or magnesium powders may give rise to concretions in the stomach (gastroliths) Bezoars may attain a large size producing symptoms simulating gastritis peptic ulcer cancer or pyloric obstruction They may occasionally simulate malignancy during roentgen examination

Treatment is indicated only when definite symptoms are present or when the foreign body presents a mechanical hazard Laparotomy with surgical re

moval may be necessary Metallic objects such as nails may be removed by means of a swallowed magnet attached to a string

Mycotic Infections of the Stomach Mycotic infections of the stomach include actinomycosis moniliasis (*Candida albicans*) aspergillosis and many others These infections frequently produce superficial or deep ulcerations of the stomach which may be single or multiple although they rarely penetrate or perforate The symptoms simulate those of gastritis ulcer or malignant disease of the stomach An examination of the vomitus or the gastric contents may reveal the fungus The treatment is that for fungus infections in general

Acute Dilatation of the Stomach Acute dilatation of the stomach is characterized by a rapid accumulation of large quantities (2 000 to 4 000 ml) of gastric and intestinal juices with marked gaseous distention of the stomach

Etiology The cause of the disease is unknown It usually occurs as a sequela of abdominal or pelvic operations or may follow abdominal trauma severe injury parturition or overeating It may complicate an acute infectious disease or be associated with uremia or marked electrolyte disturbances particularly potassium deficiency

Acute dilatation of the stomach has been attributed to the reflex inhibition of the gastric motor mechanism through efferent impulses reaching the stomach by way of the vagi and splanchnics The primary defect appears to be a loss of gastric tone followed by the swallowing of air and the accumulation of gastric and duodenal secretions which cannot be reabsorbed The gastric distention stimulates secretion further and produces pressure upon the third portion of the duodenum

Symptoms The onset is often insidious During the first 24 to 48 hr there is marked apathy and listlessness or epigastric fullness and constipation rarely with severe pain The epigastrium increases in size progressively but regurgitation and vomiting may not appear until tremendous distention has developed Although vomiting may become copious the stomach cannot empty completely Visible gastric peristalsis is absent because of gastric atony a succussion splash may be elicited Dehydration ensues associated with hypochloremic alkalosis tetany and uremia as a result of electrolyte imbalance Profound prostration collapse shock delirium coma and death follow

Diagnosis The flat roentgen film of the abdomen reveals a markedly dilated stomach filled with air and fluid permitting the differentiation from intestinal obstruction peritonitis and ileus

Treatment Treatment consists of continuous gastric suction for one day or more the administration of parenteral fluids and correction of electrolyte imbalance particularly potassium deficiency discussed in Chap 48 Recovery usually occurs if treatment is instituted promptly

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245 PEPTIC ULCER

Seymour J Gray

Definition A peptic ulcer is a benign sharply circumscribed defect or loss of tissue which extends into the muscularis mucosae or beyond and appears in areas of the alimentary tract bathed by acid pepsin gastric juice Gastric and duodenal ulcers

are considered together in this category for the sake of clarity although they may differ somewhat in regard to etiology clinical course and method of management Peptic ulcer is not merely a localized lesion of the stomach or duodenum it is a reflection of the sustained duress of our civilization manifested by emotional physiologic and biochemical aberrations which present a constant challenge to the internist psychiatrist and surgeon alike

Historical Background "Ulcer of the stomach" existed in ancient and medieval times Gastric hemorrhage was first described by Hippocrates (460 B C) In the fourth century B C Diocles of Carystos noted the adverse effects of emotional disturbances and military campaigns upon gastric ulcer A "non acid diet and sailing were recommended as treatment by Celsus in 20 A D Anatomic descriptions appeared as early as 1586 Morgagni in 1737 described perforation and gastrocolic fistula and the clinical pathologic correlations were established later by Baillie (1799) Abercrombie (1828) and Cruveilhier (1829)

Pathology The typical benign gastric ulcer presents a punched-out, sharply circumscribed lesion generally varying in size from 5 to 25 mm in diameter and from 5 to 20 mm in depth The defect appears round oval elliptical or rectangular with a flat, elevated or rounded edge depending upon the degree of edema Chronic gastric ulcers may measure 1 cm or more in depth because of thickening of the gastric wall Duodenal and jejunal ulcers are frequently smaller than gastric ulcers appearing from 2 to 10 mm in diameter and 1 to 5 mm in depth Gastric and duodenal ulcers are usually single They may occur simultaneously in both the stomach and duodenum and occasionally are multiple on the anterior and posterior walls of either organ when they are called "kissing ulcers"

Peptic ulcer begins as a penetrating process in the mucosa invading the deeper layers of the gastric wall sometimes perforating them completely It may be *acute* or *chronic* depending upon the amount of connective tissue present An *erosion* differs from an ulcer in that it involves only the mucosa and submucosa and does not penetrate into the muscularis mucosae

The base of the ulcer is usually covered by a grayish exudate of leukocytes and erythrocytes overlying a narrow layer of fibrinoid necrosis beneath which is a deeper zone of grossly red granulation tissue superimposed upon a fibrous tissue base of variable thickness The blood vessels are often thrombosed and the nerves in the scar appear edematous inflamed or necrosed The chronic ulcer undergoes repeated cycles of ulceration and healing accompanied by clinical exacerbations and remissions Scar tissue formation characterizes the healing process

Sites of Predilection Peptic ulcers occur in areas of the gastrointestinal tract exposed to the corrosive action of gastric acid and pepsin the lower esophagus stomach upper duodenum small intestine adjacent to a stoma produced during surgical anastomosis to the stomach or at the sites of heterotopic gastric mucosa in the lower end of the esophagus or in a Meckel's diverticulum The great majority of gastric ulcers are found along the lesser curvature of the stomach the *magenstrasse* a selectivity attributed by some to a diminished blood supply The pylorus itself and the immediate prepyloric area are also commonly involved Duodenal ulcers are usually found within the first 3 or 4 cm of the duodenum the duodenal bulb and are occasionally seen in the upper part of the second portion of the duodenum the so called "postbulbar" ulcer Benign gastric ulcer does not occur commonly on the greater curvature of the stomach

Incidence Approximately 10 per cent of the population develops a chronic gastric or duodenal ulcer during lifetime according to autopsy statistics It has been estimated that 1 to 3 per cent of the population above the age of twenty have some degree of peptic ulcer activity during any annual period Clinically duodenal ulcer is encountered four times as frequently as gastric ulcer although autopsy studies suggest an equal distribution

Sex There appears to be an increasing incidence of duodenal ulcer in males throughout the world since 1900 Duodenal ulcer is four times as common in men as in women although the male predominance is somewhat less in the gastric ulcer group

Age Peptic ulcer is most common between the ages of twenty and fifty although it may occur at any time Acute ulcers often multiple are seen in the newborn and perforation or hemorrhage may be the presenting symptom in the first decade of life The average age of onset for duodenal ulcer is thirty to thirty five years and for gastric ulcer thirty five to forty five years

Constitutional Type The typical ulcer patient has been classified as a tall lean hyposthenic individual Anthropometric measurements however have not been of significant predictive value and there is no specific constitutional type in this disease

Heredity Although hereditary tendencies to peptic ulcer have been noted in some families through one or more generations and ulcers have occurred in identical twins heredity does not appear to exert a primary influence

ETIOLOGY AND PATHOGENESIS

Chronic peptic ulcer in man develops presumably from a superficial erosion of a nonspecific type

Table 125 GASTRIC ACID PEPSIN AND UROPEPSIN IN NORMAL INDIVIDUALS AND PATIENTS WITH DUODENAL AND GASTRIC ULCER

	Average basal secretion mEq HCl/hr	Mean gastric pepsin units/hr	Mean uropepsin excretion units/24 hr
Normal person	1 5	18 000	3 670
Duodenal ulcer patient	5 6	50 600	8 470
Gastric ulcer patient	1 2	36 400	5 750

The acute ulceration may (1) heal promptly without scar formation (2) rapidly invade and extend through the entire gastric wall producing an acute ulcer with perforation or massive hemorrhage or (3) develop into a chronic ulcer

No single mechanism has been found for the transition of an acute erosion to an acute ulcer and its eventual development into a chronic ulcer The most pertinent factors are (1) gastric acid and pepsin (2) decreased tissue resistance (3) emotional and systemic stress

Acid Pepsin Factor Acid and pepsin are both essential to ulcer production Benign peptic ulcer occurs only in areas of the gastrointestinal tract *which are bathed by acid and pepsin and is not* found in pernicious anemia or in patients with persistent anacidity Peptic ulcer may be produced experimentally by stimulating gastric acidity with parenteral histamine in beeswax or by the continuous instillation of hydrochloric acid into the stomach

The average duodenal ulcer patient secretes acid at *more than three times the normal* rate during the basal fasting state the 12 hr nocturnal period after meals or following stimulation by histamine insulin or caffeine (Table 125) An increased secretory cell mass has been implicated A mean increase in gastric pepsin plasma pepsinogen and uropepsin is likewise seen in patients with duodenal ulcer and to a lesser extent in those with gastric ulcer Pepsin is always present in acid gastric juice acting upon cells which have been devitalized by the gastric acidity In gastric ulcer the free acid is not significantly elevated but is always present in sufficient amount to permit peptic digestion (Table 125)

Decreased Tissue Resistance The factors responsible for the tissue s resistance to ulceration are not known The *gastric mucus* acting as a barrier to ulceration as well as autodigestion may be altered or diminished *Lysozyme* a mucolytic enzyme in gastric juice does not affect the protective mucus barrier or play a significant role in peptic ulcer *Vascular factors* have been implicated because of the association of local ischemia congestion edema or venous stasis with emotional disturbances and ulcer formation It has been suggested that under conditions of stress local mucosal ischemia and ulceration may be produced by the shunting of blood through submucosal arteriovenous anastomoses Other contributing factors altering tissue resistance or increasing gastric secretion are exposure to cold anemia fatigue infections malnutrition dietary indiscretions and alcoholism

The Role of Physical and Emotional Stress in Peptic Ulcer There is considerable evidence that sustained emotional duress (anxiety fear worry and frustration) plays a significant role in the pathogenesis and recurrences of peptic ulcer Peptic ulcer appears to be a disease of civilization and is rarely seen among the natives in northern India Java and Sumatra or among the South African Bantus It is more prevalent in urban than in rural populations and among men with administrative and professional responsibilities although it occurs in all occupations and economic levels During the period of the heavy air raids on London the death rate from peptic ulcer increased as did the number of perforations and hemorrhages A similar trend was observed in Holland Sweden and Norway during the height of the war strain

Although there may not be a characteristic *personality or emotional pattern patients with peptic* ulcer have been described as overconscientious compulsive perfectionist aggressive tense stubborn critical competitive ambitious hard working and self assertive Their calm unruffled outward appearance belies the underlying suppressed mental agitation Alexander characterized the ulcer patient as a tense oral receptive" who is fundamentally dependent and wishes to remain in or revert to the infantile state This subconscious longing for the sheltered existence of the infant may manifest itself symbolically as a desire for food and milk The ulcer patient resents and is frustrated by this dependency and overcompensates by exaggerated aggression ambitiousness and independency

Hypersecretion of acid and pepsin accompanied by vascular changes within the gastric mucosa has been demonstrated during *emotional disturbance* (guilt hostility fear anger resentment and rage)

Mechanisms by Which Stress May Be Mediated to the Stomach The hypothalamus is the principal organ for the integration and transmission of emotional expression Systemic stress and emotional stimuli are expressed under cortical control through

the hypothalamus and may then be transmitted to the stomach by the vagus nerve or by an independent hormonal pathway relayed through the pituitary and adrenal glands

Hormonal Pathways Selected physical and emotional stress factors invoke a hypothalamic and pituitary response leading to the release of ACTH as part of the general adaptation syndrome ACTH in turn activates the adrenal cortex to release a number of steroid hormones including compound F which has a pharmacologic action similar to that of cortisone These adrenal steroids acting over a prolonged period may in some instances increase the gastric secretion of acid and pepsin or decrease mucus production and tissue resistance

Stimulation of the adrenal gland clinically with ACTH or the administration of adrenal steroids in therapeutic doses may in susceptible individuals (1) produce acute or chronic peptic ulcers with hemorrhage or perforation in patients with no previous peptic ulcer disease (Fig 176) (2) induce epigastric ulcerlike pain or (3) cause reactivation perforation or hemorrhage of a preexisting peptic ulcer

A relationship between the adrenal cortex and peptic ulcer is suggested by the extreme rarity of peptic ulceration and a decreased gastric secretory activity in untreated adrenal insufficiency Duodenal or gastric ulcers may develop however in patients with Addison's disease who are receiving maintenance cortisone therapy when the gastric secretory function is restored to normal Since adrenal hormone is presumably necessary for normal gastric function or for the initiation of the ulcerative process it has been postulated that the adrenal gland exerts a "permissive" action on the stomach sensitizing it to various ulcerogenic influences

Stress Ulcers Acute peptic ulcers with perforation or hemorrhage may result from increased vagal or adrenal activity or decreased tissue resistance on a vascular basis (1) *Curling's ulcer* following burns (2) *acute perforations* occurring after trauma shock or surgical procedures (3) *Cushing's ulcer* associated with intracranial diseases and (4) *air raid ulcers* are all examples of acute stress ulcers indistinguishable from those produced by the administration of adrenal steroids

Curling's Ulcer This is an acute ulceration occurring in the stomach or duodenum or both following extensive burns of the skin The lesions occur within a few days after the burn may be single or multiple and often bleed massively or perforate The ulcer may become chronic if the patient recovers A rapid increase in gastric secretion and uropepsin excretion coincides with a fall in eosinophils and increased excretion of 17 hydroxycorticoids in the urine Hemoconcentration histamine



Fig 176 Large chronic gastric ulcer 4 1 × 2 5 cm in diameter and 8 mm in depth on the posterior wall of the stomach lower third producing a massive fatal hemorrhage after 17 days of intravenous ACTH therapy (20 mg daily) A second smaller subacute ulcer 3 mm deep is seen at the left There was no previous ulcer history and routine roentgen examination of the stomach 1 year previously showed it to be normal.

release and vascular thrombosis contribute further to ulcer formation

Cushing's Ulcer This is an acute peptic ulcer with hemorrhage or perforation following brain tumors intracranial disease or brain surgery The increased gastric acidity accompanied by an elevated 17 hydroxycorticoid excretion in the urine suggests a hormonal adrenal pathway in addition to the neural mechanism

Adrenal Steroid Ulcers Acute ulcers with perforation or hemorrhage may occur during the administration of ACTH or the adrenal steroids in susceptible individuals The lesions may be single or multiple and are found in both the stomach and duodenum

ACTH and cortisone administered over a period of weeks may produce *chronic gastric or duodenal ulcers de novo* indistinguishable histologically from any other chronic peptic ulcer

SYMPTOMS OF PEPTIC ULCER

Epigastric Pain Epigastric pain is the most common presenting symptom of the uncomplicated peptic ulcer Ulcer distress may be identified by (1) rhythmic occurrence of pain following the ingestion

of food (or alkalies) (2) the character and location of the pain (3) periodicity and (4) chronicity

Mechanism of Ulcer Pain There is no unanimity of opinion regarding the cause of ulcer pain The inflammatory reaction in and around the ulcer may alter the pain threshold and increase its sensitivity Gastric acidity (chemical irritation) gastroduodenal spasm and changes in intravisceral pressure may be equally important

Rhythmic Pain Rhythmic pain following the ingestion of food or alkalies is observed in both gastric and duodenal ulcer first described by Moynihan as a food comfort pain comfort rhythm Ulcer pain almost never occurs in the morning before breakfast and characteristically appears when the stomach is empty 1 to 4 hr after a meal and persists for 30 to 60 min or more until food alkalies or water is taken Food or antacids in amounts adequate to buffer or neutralize the acid relieve the distress for 1 to 4 hr depending upon the amount ingested the rate of gastric emptying and the rate of gastric secretion

Pain after breakfast may be absent The distress is often more severe in the afternoon or between midnight and 2 A M when it awakens the patient and persists for an hour or more unless food or antacid is taken Nocturnal pain suggests hypersecretion with an acutely inflamed ulcer or pyloric edema spasm or stenosis The rhythm of gastric ulcer pain is usually less consistent than that of duodenal ulcer

Character of Ulcer Pain The character of the pain may vary in different individuals but is often described as burning gnawing cramplike aching cutting boring hurting annoying or as a hunger sensation or "gas pain" It usually persists as a steady continuous pain varying from 10 to 15 min to several hours or more differing from intermittent true hunger sensations The pain may vary from a dull ache to a sharp stabbing sensation depending somewhat on the patient s pain sensibility the extent of penetration inflammatory reaction and the location of the ulcer Uncomplicated gastric and duodenal ulcers rarely produce severe pain Duodenal ulcer pain may be more intense than gastric ulcer distress depending upon the level of gastric acidity and spasm

Duodenal ulcer pain is characteristically sharply localized to an area in the epigastrium approximately 1 in in diameter to which the patient points with the tips of two or three fingers in contrast to the generalized abdominal pain in many other forms of gastrointestinal disease The pain may radiate to the right costal margin the right lower quadrant the periumbilical area or through to the back Pain in the back usually but not invariably indicates chronic perforation into the head of the pancreas Gastric ulcer pain may be located in the left epigastrium while jejunal ulcer distress is more common in the midabdomen or left lower quadrant

Periodicity One of the most classic features of the peptic ulcer syndrome is the tendency for ulcer pain to disappear spontaneously for periods of 6 months to a year or longer The disappearance of symptoms is usually associated with a remission in the disease process and the recurrence of pain with a reappearance of the ulcer

Seasonal recurrences of peptic ulcer have often been noted in the late fall and early winter and again in the spring but these remain unexplained Fluctuations in gastric acidity corresponding roughly to the seasonal variation of the disease have been observed by Vanzant The influence of fatigue infection tension anxiety temperature changes and other forms of stress subject to seasonal variation may be significant Fluctuations in the threshold of adrenal activity and hormonal influences throughout the year may play a role although this has not as yet been proved

Chronicity The chronicity of the disease is often established by careful history In some instances the symptoms may have existed for only a few weeks particularly in the younger age group In others careful questioning will reveal an intermittent ulcer history of 10 to 20 years with many spontaneous remissions and exacerbations

Atypical Ulcer Symptoms When hypersecretion with gastritis duodenitis pyloric spasm or obstruction supervene ulcer pain may be only partially relieved by antacids or food Complete relief of pain follows aspiration of the stomach or more complete neutralization of the acid In some instances the discomfort is described as a *nausea sensation* *Vomiting* is rare in the uncomplicated ulcer and is often self induced to relieve pain A rare variant of the ulcer syndrome known as the *tabetic* or *biliary* type of pain is characterized by severe steady pain with persistent vomiting similar to that seen in biliary colic or tabetic crisis *Water brash* is an uncommon complaint of acid regurgitation and excess salivation occurring occasionally at night Other symptoms include gaseous discomfort or a cramplike distress when the stomach is empty *Constipation* and *irritable bowel symptoms* are common *Diarrhea* is rare except as a complication of gastrojejunocolic fistula *Weight loss* is unusual unless there is obstruction *Anemia* may develop gradually from chronic blood loss or acutely from massive hemorrhage

DIAGNOSIS

The diagnosis of peptic ulcer is made from the clinical history physical findings and particularly the roentgen or gastroscopic demonstration of the ulcer

Physical Examination The physical examination may reveal no significant abnormalities In some instances localized superficial or deep tenderness with muscle guarding may be elicited in the epigastrium between the xiphoid cartilage and the umbilicus A tender mass is rarely palpable The physical findings associated with perforation and obstruction will be discussed in the section on complications

Laboratory Examination Although the presence of free hydrochloric acid in the gastric contents is essential to the diagnosis of benign gastric ulcer instances of histamine anacidity with benign ulcers have been reported All lesions associated with persistent histamine achlorhydria should be considered malignant until proved otherwise The volume and concentration of gastric acidity in the individual patient, however is not diagnostic for either gastric or duodenal ulcer although the acidity is often increased in the latter Uropepsin excretion and plasma pepsinogen are significantly elevated in duodenal ulcer (Table 125) although they may be increased under other conditions as well Occult blood is frequently found in the gastric juice or stools of patients with active peptic ulcer The finding of sarcinae or yeast cells in the gastric contents suggests stasis and long continued obstruction Leukocytosis is sometimes observed particularly in the presence of vomiting dehydration or hemorrhage

Roentgen Examination The roentgen examination is the most valuable procedure in the diagnosis of peptic ulcer and constitutes an integral part of the examination of patients with epigastric distress

The visualization of a niche or crater in the stomach is pathognomonic of an ulcerating lesion Gastric ulcer appears as a smooth regular ulcer niche appearing in profile as a projection extending from the lesser curvature of the barium filled stomach (Fig 177) An active duodenal ulcer presents a crater and is usually seen *en face* as a sharply outlined, circumscribed collection of barium usually 2 to 10 mm in diameter standing out in contrast to the surrounding barium in the area (Fig 178) At times centrally radiating rugal folds converge to the site of the ulcer Craters may occur in the stomach duodenal bulb or the second portion of the duodenum The duodenal ulcer scar may contract one or both curvatures of the duodenal bulb producing a typical cloverleaf deformity (Fig 179) The healed gastric ulcer rarely distorts the stomach except in cases of chronic gastric ulcer when an hourglass deformity may result

Gastroscopic Examination The benign gastric ulcer appears as a sharply punched out lesion without evidence of nodularity or stiffness Its appearance may be helpful in distinguishing benign from malignant lesions Ulcers distal to the pylorus cannot be visualized gastroscopically

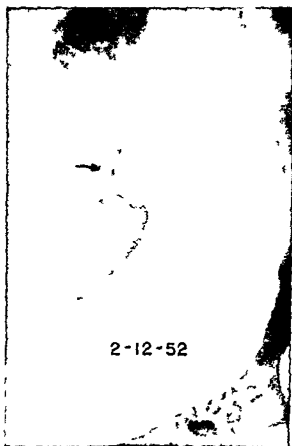


Fig 177 Large benign gastric ulcer on the lesser curvature of the stomach which healed completely in 10 weeks in a 6? year-old man The stomach was resected – months later because of an associated duodenal ulcer and revealed a small healed residual scar

The Differential Diagnosis of Benign from Malignant Gastric Ulcer The differentiation of benign from malignant lesions is often exceedingly difficult and depends upon a combined evaluation of all available clinical laboratory roentgenologic, and gastroscopic criteria The differentiation based on clinical history alone is usually not possible Although cancer often occurs in an older age group presents a shorter history or a change in character of the chronic distress none of these criteria is sufficiently distinctive in any individual to be diagnostic

The rhythmic postprandial distress with relief by antacids which characterizes the benign ulcer may occur with gastric cancer as well although complete relief of pain is uncommon Anorexia and weight loss occur more often in cancer usually late in the disease Vomiting of blood and melena are more common in ulcer but are not infrequent in cancer

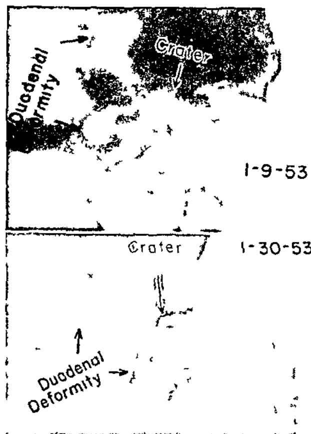


FIG 178 Large duodenal ulcer crater in a 52 year old woman demonstrating radiating folds duodenal deformity and pseudodiverticulum formation The crater healed in approximately 3 weeks

The presence or absence of anemia is not diagnostic of either disease

Laboratory Examinations Laboratory studies are helpful but often not conclusive *Persistent occult blood* in the stools after 2 or 3 weeks of treatment in a patient with a gastric lesion suggests malignancy although persistently negative stools are seen frequently with cancer Chronic gastric ulcer may also produce positive stools for occult blood intermittently for many weeks in spite of good treatment *A persistently low uropepsin excretion* is presumptive evidence of malignancy in a patient with a gastric lesion although a normal or high excretion does not exclude cancer (Table 124 Chap 244) *Persistent histamine anacidity* indicates malignancy although normal or high acidity may occur with cancer *Exfoliative cytology* may be exceedingly helpful in the diagnosis if tumor cells are found A negative cytology does not exclude malignancy

Roentgen Criteria Presumptive roentgen evidence of malignancy includes the following points

1 An ulcer crater surrounded by a collar of rigid tissue located beneath the contour of the lesser curvature with stiffness and induration on fluoroscopic examination (meniscus sign of Carman Fig 172 Chap 244) Edema and inflammation about a chronic benign ulcer may simulate malignancy although the ulcer niche of the benign ulcer usually extends beyond the level of the lesser curvature (Fig 177)

2 Ulcers on the greater curvature of the stomach are often but not invariably malignant

3 Stiffness and irregularity of the ulcer area

4 An ulcer associated with a filling defect marked rigidity or induration

5 Persistence of the ulcer or incomplete healing after adequate treatment

Benign lesions are characterized by the following

1 Converging or radiating folds to the site of the ulcer (in malignant lesions these are interrupted or absent)

2 Smooth contour and pliable sharp borders

3 Disappearance of the lesion on treatment with no residual evidence of ulcer infiltration or impairment of peristaltic activity

The size of the ulcer is of no diagnostic value large ulcers are frequently benign The site of the ulcer may be significant Lesions of the greater curvature are often malignant ulcers at the cardia have a greater incidence of malignancy than more distal lesions of lesser curvature Antral and pre

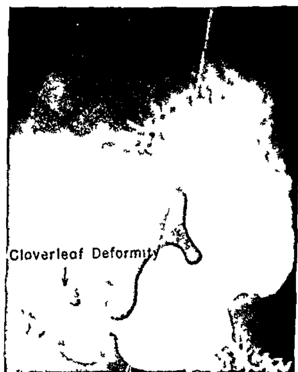


FIG 179 Typical cloverleaf deformity of the duodenal bulb with contraction of both curvatures produced by a duodenal ulcer scar

pyloric ulcers are often benign although predisposition of this area to malignancy has been reported

Gastroscopic Criteria Malignancy is suggested by (1) stiffness nodularity or induration of the ulcer edge (2) absence of a sharply demarcated clean-cut ulcer border resulting in blending with the surrounding mucosa (3) an elevated nodular stiff rolled up cuff of tissue surrounding the ulcer (4) absence of radiating folds and (5) extensive gastric atrophy These criteria are of presumptive value

Summary A definitive and unequivocal diagnosis of benign gastric ulcer cannot be made by the clinical history laboratory techniques or roentgen and gastroscopic examinations A reasonably accurate *presumptive* or *tentative* diagnosis of benign gastric ulcer can be made however by combining these diagnostic criteria The only conclusive evidence of a benign process is the complete healing of the ulcer by roentgen and gastroscopic examination (The management of gastric ulcer is discussed on p 1445)

Development of Cancer from Benign Ulcer Duodenal ulcers do not undergo malignant change Primary carcinoma of the first portion of the duodenum is exceedingly rare The possibility of malignant transformation of a benign gastric ulcer however cannot be categorically proved or refuted There is considerable evidence that a benign gastric ulcer very rarely becomes malignant In most instances the carcinomatous ulcer originates as a gastric neoplasm which undergoes ulceration as a result of peptic digestion or necrosis and simulates a benign lesion

Differential Diagnosis of Ulcer Distress A number of disease processes may simulate ulcer distress particularly if the symptoms are atypical (1) gastritis and duodenitis (2) hiatal hernia (3) gallbladder disease (4) coronary heart disease (5) carcinoma of the stomach or esophagus (6) esophageal ulcer (7) cardiospasm (8) irritable colon (9) pancreatitis (10) appendicitis (11) peptic ulcer in Meckel's diverticulum and (12) diseases of the kidney urinary tract and pelvic organs

Relationship to Other Diseases Peptic ulcer may coexist with many diseases except those associated with histamine achlorhydria such as pernicious anemia and extensive gastric atrophy It is rare in untreated Addison's disease a fact which emphasizes the significance of the hormonal mediation of stress to the stomach Peptic ulcer is rarely encountered in pregnancy although both hemorrhage and perforation may occur A healed doudenal ulcer deformity may be seen in patients with gastric cancer but the association of an *active* ulcer crater with a separate cancer is rare Peptic ulcer frequently occurs in patients with hiatal hernia and it may be increased with cirrhosis of the liver It is not more frequent in gallbladder disease diabetes and cardiovascular disease than in the population at large An increased incidence of peptic ulcer probably exists in polycythemia suggesting the relationship of vascular thrombosis to the pathogenesis of the disease

MEDICAL MANAGEMENT

A myriad of drugs and treatments are regularly heralded as "the ulcer cure" only to be added to a growing list of therapeutic failures Spontaneous periodic remissions in the disease process symptomatic improvement without ulcer healing and the psychologic benefits of an enthusiastic new therapeutic approach make clinical evaluation difficult Since no single etiologic factor in the pathogenesis of peptic ulcer has been established no ulcer cure may be anticipated The most satisfactory ulcer regimen is based upon a therapeutic approach to the secretory neurogenic hormonal and psychosomatic factors in the disease

General Principles of Therapy Therapy of peptic ulcer is directed to the healing of the ulcer and the prevention of recurrences Adequate acid neutralization at the ulcer site and attention to the physical and emotional stress factors which may promote acid secretion and spasm are the fundamental principles upon which effective ulcer management is based

Sippy's original premise that "the greatest known hindrance to the healing of peptic ulcer is the disintegrating and digestive action of the gastric juice" is still true Compounds designed to neutralize or inhibit the output of hydrochloric acid constitute a major part of the present therapeutic approach

Just as important as acid neutralization is the recognition by both the physician and patient of the psychologic and fatigue factors involved in the disease from the standpoint both of treatment and of prevention of recurrences The patient must be oriented to the chronicity of the disease and reeducated to "live with the ulcer" with minimal restrictions

Doctor Patient Relationship Successful therapy often depends upon an understanding physician who will help in coping with family difficulties poor eating habits sex problems financial worries adverse working conditions and social ambitions In selected cases formal psychiatric care including psychoanalysis may prove helpful but this is the exception rather than the rule Both psychotherapy and medication have a definite place in the management of peptic ulcer and the internist is qualified to administer both in most instances

Change of Environment Physical and mental rest are essential to healing The tense anxious and resentful patient may benefit from a short period of hospitalization or a vacation for 1 to 2 weeks Many patients do not require hospitalization or protracted removal from the home or work environment but are advised to interrupt *sustained* emotional stress and anxiety by frequent short vacations All patients with gastric ulcer should be hospitalized for a brief period to exclude malignancy by all available diagnostic procedures and to ensure the most rapid healing possible

Sedation Sedation in the form of phenobarbital in small divided doses throughout the day (15 to 30 mg) is very effective and should be part of the routine management Sedatives do not exert any direct effect on gastric secretion but they decrease the stream of impulses which pass from the higher centers of the brain to the stomach The new tranquilizing drugs (meprobamate) in small divided doses may be helpful also

Control of Gastric Acidity The aim of antacid therapy is the effective neutralization of gastric acidity and reduction in peptic activity Effective neutralization may be defined as the maintenance of the pH at 4 0 to 5 5

Aluminum Hydroxide The aluminum hydroxide preparations the safest and most satisfactory of the antacids in common use react with gastric hydrochloric acid to form aluminum chloride and water and are excreted in the feces as aluminum phosphate Although the final pH of the gastric juice usually does not exceed 4 0 aluminum hydroxide is an effective antacid demulcent and adsorbent

During the acute phase of ulcer disease liquid preparations in dosage of 15 to 30 ml hourly (or larger doses in cases of marked hypersecretion) are preferable Once the patient has become ambulatory the tablet form may be more convenient The dose varies from 2 to 4 tablets every 1 to 2 hr

Calcium Carbonate Calcium carbonate may prove beneficial in selected patients with marked hyperacidity and rapid gastric emptying who may not respond to the aluminum hydroxide preparations Hourly doses of 2 to 4 Gm are recommended Calcium carbonate is converted to calcium chloride in the stomach and excreted in the stools as relatively insoluble calcium phosphate and carbonate

Sippy Powders The Sippy powders neutralize gastric acidity more effectively than any other antacid they are prepared by mixing calcium carbonate and sodium bicarbonate in ratios of 1 1 to 1 4 They are usually administered in doses of 2 Gm hourly or every 2 hr

Other Antacids Numerous other preparations which inhibit pepsin activity or decrease gastric acidity by partial neutralization buffering and demulcent action or anion absorption have no advantages over the more effective less expensive antacids mentioned above These include magnesium trisilicate and carbonate protein hydrolysate sodium carboxymethylcellulose mucin anion exchange resins and detergents

Antacid Therapy Aluminum hydroxide preparations are not absorbed from the intestinal tract do not disturb the acid base balance and may be used safely in the treatment of most patients with peptic ulcer Calcium carbonate and the Sippy powders are contraindicated in the presence of (1) vomiting or repeated gastric aspirations (2) renal cardiac or liver disease and (3) hypertension because of the dangers of sodium absorption and hypochloremic alkalosis

The antacids should be administered at frequent and regular intervals since the rate of ulcer healing depends upon the duration and constancy of acid neutralization The antacids are prescribed at hourly intervals during the day and every 2 hours during the night with milk and cream feedings for the first week or two The management is not considered adequate unless the patient is completely free of pain When the symptoms subside antacid therapy may be administered at 2 hour intervals for 4 to 8 weeks until the ulcer has healed and is then prescribed four times daily between meals and twice in the evening particularly at bedtime All the antacids may produce severe constipation usually prevented by the use of magnesium oxide or carbonate (2 to 4 Gm) milk of magnesia (15 to 30 ml) or other mild cathartics

COMPLICATIONS OF ANTACID THERAPY *Fecal impactions* are common with all forms of antacid therapy particularly in the aged and bedridden and may be prevented by mild cathartics oil retention enemas and frequent rectal examinations

Hypochloremic alkalosis following vomiting or repeated aspiration of highly acid gastric juice containing 115 to 125 mEq per liter of chloride is seen in patients with gastric retention or obstruction Alkalosis from prolonged intake of absorbable alkalies such as the Sippy powders is becoming less common since the advent of aluminum hydroxide preparations and usually occurs in patients with previous kidney damage Symptoms of alkalosis are often absent although weakness lassitude headache loss of appetite nausea vomiting and clouding of the sensorium may be observed The blood carbon dioxide content is elevated and chlorides are depressed Secondary renal failure is manifested by a sharp rise in the blood urea nitrogen Treatment consists of discontinuance of alkalies and replacement of oral or parenteral chlorides and fluids discussed in Chap 48 In some instances of severe alkalosis the use of intravenous ammonium chloride has proved of great value A 2 per cent solution in distilled water or physiologic saline solution may

be administered slowly at a rate of not more than 200 ml per hr The use of ammonium chloride is contraindicated in the presence of liver disease

Renal calcinosis is a rare complication occurring in patients with previous kidney damage who take excess absorbable alkalies and milk for many years It is characterized by *hypercalcemia* without hypercalcuria or hypophosphatemia normal serum alkaline phosphatase renal insufficiency and alkalosis Treatment consists of avoidance of alkalies calcium restriction and forced fluids

Renal Calculi An increased incidence of renal stones following prolonged absorbable alkali therapy probably exists but has not been definitely established and is less common since the use of aluminum hydroxide therapy

Diet The ulcer diet consists of frequent regular feedings of small amounts of bland nonirritating foods the proteins of which buffer the hydrochloric acid and thus serve as effective antacids In addition to the milk proteins the hourly milk and cream feedings (Table 126 Ulcer Diet I) provide fat which supplies calories and reduces gastric secretion and motility In some instances whole milk or skimmed milk may be substituted for milk and cream and syrups or malt may be added for flavor If the milk or calcium intake must be limited as in patients with kidney stones or renal calcinosis gelatin or Jell-o may be substituted

The patient may complain of the monotony of this diet however and few need to be restricted to it for very long. Bread butter cereals cheese macaroni rice noodles potatoes eggs custards ice cream Jell-o and other soft foods may be added to or substituted for the hourly milk feedings from the start of treatment in many instances (Table 126 Ulcer Diet II) Regularity and frequency of meals are as important as the choice of food The diet is supplemented by vitamins

The patient is instructed to follow a specified schedule of feedings between meals individualized on the basis of his daily routine Unless the dietary pattern tastes food idiosyncrasies working hours and emotional factors are considered the patient will not follow a dietary regimen

During the healing process dietary discretion is difficult for many patients without the personal supervision and encouragement of the physician Gradual liberalization of the diet (Table 126 Ulcer Diets III and IV) to a three meal regime is recommended usually within 2 to 3 weeks The milk and cream or small feedings should be continued between meals together with the antacids After healing has occurred (4 to 8 weeks) a liberal bland diet is prescribed (Table 126 Ulcer Diet IV) with interval feedings three to four times daily

Alcohol a powerful stimulant of gastric acidity is not permitted during the active stages although

Table 126 ULCER DIETS

Ulcer Diet I

45 to 60 cc milk
45 to 60 cc cream (20% cream)
90 to 120 cc of above mixture every hour from 7 A M to 10 P M (1970 to 2660 cal 45 to 60 Gm protein)
If necessary additional feedings of 240 cc of the above mixture are given at 12 midnight 2 A M and 4 A M (950 additional calories 34 additional Gm protein)

Ulcer Diet II

45 to 60 cc milk
45 to 60 cc cream (20%)
90 to 120 cc of above mixture every hour from 7 A M to 10 P M
Small equal meals are given at 2-hr intervals from 8 A M through 10 P M Food is chosen from the following list
Cereals—refined or strained (Cream of Wheat oatmeal boiled rice)
Eggs—soft-cooked poached scrambled creamed
Toast or cracker—white only
Cheese—mild American cottage cream
Potato—white mashed or baked
Spaghetti noodles macaroni rice—all may be creamed au gratin buttered escalloped
Cream soups—strained
(rice pea potato celery mushroom spinach)
Jell-o custard plain puddings (butterscotch caramel tapioca Bavarian cream blancmange rice bread gelatin)
Vanilla ice cream
Butter or margarine

Ulcer Diet III

3 meals—8 A M 12 noon 6 P M—and 3 interval feedings—10 A M 3 P M 10 P M from the following list of foods
Cereal—refined or strained
Bread toast crackers—white light rye
Eggs—soft-cooked poached creamed scrambled
Cheese—mild American cottage cream
Meat poultry—ground beef veal lamb mutton broiled liver sliced turkey or chicken
Fish—fresh cod haddock sole halibut
Vegetables strained or puréed—asparagus carrots beet peas spinach green or wax beans squash
Potato white mashed or baked
Spaghetti noodles macaroni rice—all may be creamed au gratin buttered escalloped
Cream soups—rice pea potato celery mushroom spinach
Fruit soft-cooked canned or puréed—pears peaches *peeled apricots Royal Ann cherries* applesauce stewed apricots peeled apples prunes prune juice
Desserts—Jell-o custard puddings fruit whip ice cream, plain cake cookies (as listed in *Ulcer Diet II*)
Butter or margarine
One cup of coffee tea or Sanka
90 to 120 cc milk and cream mixture hourly between feedings or milk alone

Table 126 ULCER DIETS (*Continued*)

Ulcer Diet II

3 meals—8 A M 12 noon 6 P M —and 3 interval feedings—10 A M 3 P M 10 P M —from the following list of foods

Cereals—well cooked or refined ready to-eat

Bread toast and crackers—white and light rye fine graham

Eggs—soft-cooked or poached creamed scrambled

Cheese—mild American cottage cream

Meat poultry tender cuts baked broiled creamed roasted—beef steak veal lamb mutton liver turkey chicken

Fish—fresh cod haddock sole halibut (shellfish—optional depending on tolerance)

Vegetables—soft-cooked or canned (same choice as in Ulcer Diet III)

Potato—white mashed or baked

Spaghetti noodles macaroni rice

Cream soups—as in Ulcer Diet III plus any cooked vegetables as listed above

Fruits—soft-cooked or canned * (same choice as in Ulcer Diet III)

Desserts—same choice as in Ulcer Diet III

Butter or margarine

Tea coffee or Sanka

240 cc milk or milk and cream mixture every 2 hr between meals or as substitute for interval feedings

* Diluted orange juice after meals is optional

the tense individual with a healed ulcer may be allowed a very limited amount with meals

Coffee tea and chocolate are also stimulants of gastric acidity and should be restricted to a total of 1 to 2 cups daily with cream after meals During the acute ulcer phase a more strict limitation is advisable Decaffeinated beverages are well tolerated

Smoking There is no clinical or laboratory evidence that 8 to 10 cigarettes daily alter the course of the disease but excessive smoking should be discouraged particularly in patients with spasm or gastric retention The frustration of a habitual smoker deprived of tobacco may counteract the possible benefits to be derived from complete restriction In some patients however complete withdrawal is necessary

Aspirin may cause gastric irritation and should be avoided

Antisecretory Drugs A number of drugs are available which block the transmission of vagal impulses to the stomach and consequently reduce gastric acidity and motility These compounds supplement and complement antacid therapy

Atropine and *belladonna* are the most commonly used cholinergic blocking agents inhibiting the secretory and motor activity of the stomach The drugs appear to block the action of acetylcholine at the neurocellular junctions of the postganglionic vagal nerve endings Atropine is prescribed in doses of 0 3 to 0 6 mg and tincture of belladonna in doses of 8 to 20 drops in water (depending upon tolerance) four times daily before meals and at bedtime Inhibition of gastric secretion is usually accompanied by mild toxic symptoms such as dryness of the mouth or blurring of vision Full tolerance doses just short of these symptoms are desirable Numerous atropinelike compounds have been synthesized in an attempt to reduce the toxic side effects without altering the antisecretory activity These medications are generally more expensive and not more effective than atropine and belladonna Methantheline bromide (Banthine—50 to 100 mg four times daily) and propantheline bromide (Probanthine—15 mg four times daily) have no advantages over adequate doses of atropine

Dryness of the mouth blurring of vision tachycardia and urinary retention are the most common side effects Other toxic symptoms include drowsiness headaches constipation and manifestations of central nervous system stimulation This medication is contraindicated in coronary insufficiency cardiac disorders glaucoma and prostatic hypertrophy

Treatment of Intractable Ulcer Pain Patients may continue to experience ulcer pain in spite of a satisfactory dietary antisecretory and antacid regime Persistent intractable pain is usually associated with (1) an ulcer in the pylorus or duodenum (2) pyloric spasm edema or cicatrization (3) a penetrating ulcer and (4) marked nocturnal hypersecretion Additional measures are directed towards the removal or neutralization of gastric acidity

Gastric Aspiration Gastric aspiration is a most valuable adjunct to antacid therapy particularly in patients with night pain Continuous gastric aspiration for 24 to 36 hr is indicated in the presence of intractable pain with persistent vomiting or pyloric obstruction Prolonged aspiration is avoided because of the danger of hypochloremic alkalosis and because of discomfort to the patient

Soluble Alkalies Sippy powders or calcium carbonate (2 Gm every 1 to 2 hr) often relieves pain which has been intractable to aluminum hydroxide these soluble alkalies are useful for short periods in selected patients if there are no contraindications

Control of Nocturnal Secretion A marked increase in nocturnal secretion may produce night pain delayed healing gastric hemorrhage or perforation The pain is often relieved by administering aluminum hydroxide or the soluble antacids (Sippy powder calcium carbonate) at 2 hr intervals throughout the night with simultaneous feedings of 250 cc of milk and cream Atropine sulfate in doses of 0 6 to 1 mg at 6 00 P M and 10 00 P M and

nightly aspiration at 10 00 P M are particularly effective

Continuous Drip Therapy Continuous drip therapy is rarely necessary if the patient is awakened at 2 hr intervals during the night for regular feedings of milk cream and antacids In unusual instances where frequent feedings are refused food and antacids may be administered through a nasal catheter by a continuous drip The Winkelstein formula consists of 1 liter of milk containing 5 Gm sodium carbonate during every 8 hr period

Radiation Therapy Radiation therapy to the stomach *may inhibit gastric secretion* and facilitate healing in selected patients with intractable ulcer pain uncomplicated by pyloric obstruction Inhibition of gastric secretion is variable and usually not permanent *Two treatments are given* daily for 10 days through alternating anterior and posterior portals 13 cm square for a daily depth dose of 165 roentgens (r) (calculated in the midplane of the gastric fundus) and a total exposure of 1 650 r

Treatment of Gastric Ulcer All gastric ulcers should be considered potentially malignant until proved benign *A trial of medical management* for 4 to 8 weeks with sedation diet antacids and antispasmodics is justified when a classically benign gastric ulcer (by clinical roentgen and gastroscopic criteria) is found in a patient with free gastric acidity and a normal or high uropepsin excretion Hospitalization is usually advisable and *the course of the disease should be followed carefully* by repeated examinations

If the ulcer does not heal completely as shown by roentgen and gastroscopic examination after 4 to 8 weeks of satisfactory medical management or if abdominal pain or occult blood in the stools persists surgical exploration is indicated

Immediate surgery for gastric ulcer is recommended when (1) there is a reasonable doubt of the diagnosis clinically or by roentgen and gastroscopic examination (2) a meniscus sign or filling defect is present (3) the cytologic examination is positive (4) *histamine anacidity or a persistently low uropepsin excretion exists* (5) the ulcer is located on *the greater curvature of the stomach*

Subtotal gastric resection is the operation of choice for gastric ulcer and is indicated when the ulcer recurs under medical management or when there is difficulty in establishing the benign nature of the lesion The recurrence rate following resection for gastric ulcer is exceedingly low

Indications for Surgery Surgery is necessary in 10 to 20 per cent of patients with peptic ulcer because of intractability hemorrhage perforation or obstruction *In the uncomplicated duodenal ulcer* surgery is indicated when the patient appears unwilling or unable to follow an ulcer regime or when *frequent recurrences constitute an economic burden*

Subtotal gastrectomy for duodenal ulcer is the most satisfactory surgical procedure with a recurrence rate of approximately 5 per cent and a mortality rate of 2 to 3 per cent Gastroenterostomy *has been followed by recurrent ulcers in 20 to 30* per cent of patients in some series it is performed in elderly patients who are poor surgical risks or when a gastric resection is not feasible technically *Vagus section alone is not a satisfactory procedure* in view of the high incidence of recurrent ulcer (10 to 15 per cent) and other side effects Combination of vagus section with gastroenterostomy or gastrectomy is still being evaluated *The recurrent* ulcer rate is 5 to 15 per cent and will probably increase after a longer follow up period

Prognosis Approximately 80 per cent of ulcer patients respond satisfactorily to medical management over a period of years although the disease is characterized by remissions and exacerbations The *recurrence rate varies from 10 to 30 per cent* during the first year increasing thereafter by approximately 10 per cent each year depending upon emotional factors and the patient s adherence to a medical regime *Recurrences are attributed to fatigue* emotional and physical duress infections and indiscretions in diet alcohol coffee or tobacco

COMPLICATIONS OF PEPTIC ULCER

Perforation

Acute perforation is a serious complication occurring in 2 to 10 per cent of peptic ulcer patients and is a *common cause of death from this disease* It is exceedingly rare in women the male preponderance being 49 1 Perforation of a duodenal ulcer occurs nine times more commonly than that of a gastric ulcer *It may occur in any age group* but is usually observed in patients under forty five years The most common site of perforation is the *anterior wall of the duodenum*

A history of antecedent ulcer disease is present *in 75 per cent of cases* and *previous hemorrhage* is observed in 10 to 20 per cent Simultaneous hemorrhage and perforation are rare *Recurrent perforation* may occur in 1 to 5 per cent of perforated ulcers

Symptoms The perforation is heralded by a sudden agonizing excruciating pain in the midepigastrium accompanied frequently by collapse The pain *may remain localized but usually spreads to* the entire abdomen Radiation to the right *shoulder* may be present as a result of irritation of the diaphragm by free air or gastroduodenal contents Although the patient may be ashen gray and covered with a cold sweat as in surgical shock the blood pressure is usually normal and the pulse rate elevated *only slightly* Nausea and retching are

almost always present but vomiting may be a late symptom Body temperature at the onset is normal or subnormal

The patient lies "rigid and motionless The abdomen is immobile and the muscles are taut and rigid particularly in the upper portions producing classic boardlike rigidity The extent of rigidity depends upon the amount of gastric contents which has escaped into the peritoneal cavity Tenderness is usually generalized becoming most marked in the upper abdomen and occasionally spreading to the right lower quadrant as a result of drainage down the right lumbar gutter This localization presents the problem of differentiating perforation from acute appendicitis

After an hour or two the pain decreases muscle spasm remains the body becomes warm and the skin may regain its normal color If surgery is not performed at the end of 12 to 24 hr generalized peritonitis usually develops characterized by fever an increasing pulse rate leukocytosis and distention of the abdomen with loss of the boardlike rigidity but persistence of generalized tenderness

Physical Examination During the acute phase of perforation physical examination reveals in addition to the boardlike rigidity of the abdomen absent peristaltic activity and occasionally diminished liver dullness A subphrenic or subhepatic abscess may present itself 5 to 10 days following perforation as a mass or area of tenderness in the right upper quadrant accompanied by fever

Roentgen Examination Roentgen examination of the abdomen demonstrates pneumoperitoneum in more than two thirds of the cases of acute perforations best elicited if the patient is sitting up or lying on the left side for a few minutes prior to roentgenography Air when present is seen beneath the diaphragm or the lateral abdominal wall

Differential Diagnosis The most difficult differentiation is that of *acute pancreatitis* where there is usually more severe shock vomiting is more frequent and the abdominal rigidity is less intense and not boardlike Pneumoperitoneum is not present Pancreatitis is much more common in women than acute perforation A history of biliary tract disease is often present A markedly elevated serum amylase usually above 600 Somogyi units is frequently observed during the attack of acute pancreatitis although moderate increases in amylase may also occur with a perforated peptic ulcer Laboratory examination in acute pancreatitis may also reveal an increase in urinary diastase serum lipase blood sugar serum bilirubin or glycosuria

Acute appendicitis may be confused with perforated ulcer although the onset of pain is less sudden the rigidity is less intense and the past history of ulcer pain is often lacking There is no shoulder tip pain and the prostration is minimal Tenderness is maximal in the right lower quadrant less marked in the upper abdomen and may be present on rectal examination In *biliary or renal colic* the frozen attitude of the patient and the boardlike rigidity of the abdomen are absent If the gallbladder perforates the ensuing generalized peritonitis may mimic a perforated ulcer *Perforation of the gallbladder* however usually occurs during or after acute cholecystitis which first produces severe localized pain In *mesenteric occlusion* and *intestinal obstruction* the pain is often colicky and intermittent associated with some distention slight rigidity and more frequent vomiting The pain and tenderness of a *ruptured ectopic pregnancy* are usually in the lower abdomen and the rigidity is only moderate In *coronary occlusion* there is no marked rigidity of the abdomen and the pain radiates to the sternum neck and arms Abdominal rigidity is also absent in *gastric crisis* of tabes dorsalis The pain of *dissecting aneurysm* of the aorta is commonly substernal and intense *Diaphragmatic pleurisy* and *basal pneumonia* occasionally produce abdominal and shoulder pain associated with upper abdominal spasticity and tenderness but the cough fever increased respiratory rate and localization of pain to the upper abdomen are significant differential factors

Treatment Acute perforation constitutes a surgical emergency if the patient is seen within the first 24 to 48 hr after the perforation The mortality rate is lowest if surgery is performed within the first 6 to 12 hr Simple closure by suture with or without omental graft is the usual procedure Treatment for shock if present is instituted along with constant gastric suction antibiotic therapy and supportive electrolyte plasma and fluid administration

If more than 24 to 48 hr have elapsed after the perforation conservative management is generally recommended Decompression of the stomach with an indwelling tube is instituted at once and intensive chemotherapy is begun Similar conservative management is applied to patients in whom spontaneous closure of the perforation has already occurred as evidenced by the rapid disappearance of the pain the sharp localization of tenderness and rigidity and the excellent clinical state of the patient

Since the advent of antibiotics the mortality from acute perforation is probably less than 6 per cent Recently conservative management has been recommended as the definitive treatment for acute perforations and a mortality rate of 5 per cent or lower has been reported but the routine use of this form of therapy has not been widely accepted

Since perforation usually occurs in the severe

and often intractable forms of peptic ulcer with only 20 per cent remaining asymptomatic subtotal gastric resection as an elective procedure at a later date should be given serious consideration

Subacute and Chronic Perforations

Subacute and chronic perforations occur in the medial wall of the duodenum in contrast to the acute perforations of the anterior surface Consequently there may be little or no spillage of intestinal contents Free perforations into the peritoneal cavity occur but these are spontaneously sealed by fibrinous adhesions to the omentum liver and pancreas resulting in recovery without surgical intervention Diagnosis of these so called *forme fruste* perforations may be difficult since the symptoms are mild and atypical The patient may complain of sudden severe upper abdominal pain which within a few hours develops into a mild dull ache The amount of leakage is minimal producing a localized receding right upper quadrant peritonitis In some instances small abscesses may be formed at the ulcer site or under the diaphragm Physical signs consist of right upper quadrant tenderness and spasticity Roentgenograms may or may not show free air in the peritoneal cavity Many of these patients recover without any specific treatment although surgical intervention is recommended once the diagnosis has been made

In chronic perforation the capsule of the pancreas or liver or the transverse mesocolon or colon forms the base of the ulcer and no free perforation into the peritoneal cavity occurs Abscess formation is uncommon This type of perforation is rarely diagnosed except when a jejunal ulcer perforates into the colon producing diarrhea as the presenting symptom

Massive Hemorrhage

Approximately 20 to 25 per cent of all patients with peptic ulcer experience some degree of bleeding during the course of the ulcer Massive bleeding as hematemesis (vomiting of gross blood) or melena (tarry stools) occurs in 10 to 20 per cent of ulcer patients rarely in women Peptic ulcer is responsible for from 60 to 75 per cent of upper gastrointestinal bleeding

Contributing factors in massive gastric hemorrhage include alcoholism undue physical or emotional stress hypertension and arteriosclerosis excess aspirin intake infections fatigue dietary indiscretions and prolonged use of cortisone or adrenocorticotropic hormone

Pathology of Bleeding Ulcer Bleeding may be the result of ulceration into an artery vein or capillary Fatal hemorrhage is usually arterial in origin resulting from erosion into the pancreaticoduodenal gastroduodenal or gastric coronary artery or their larger branches A rigid arteriosclerotic vessel in the scar tissue of the ulcer base may be responsible for the fatal hemorrhage

Symptoms The signs and symptoms depend upon the severity of the hemorrhage the rate of bleeding and the suddenness of onset Hematemesis signifies a more rapid and extensive form of hemorrhage than melena Hematemesis is commonly observed in gastric ulcer but occurs in only 20 to 25 per cent of patients with duodenal ulcer Blood loss varies from the 60 ml necessary to produce a tarry stool to well over 1 000 ml The passage of a tarry stool may be the only presenting symptom since the loss of 350 to 500 ml of blood into the intestine may cause no significant change in the dynamics of the circulation if the hemorrhage has not occurred too rapidly

The symptoms following massive bleeding are faintness weakness dizziness headache perspiration thirst dyspnea syncope pallor and shock The pulse is usually rapid and weak The blood pressure is normal or low depending upon the patient's ability to compensate for the blood loss A persistently low blood pressure and a weak rapid pulse signify a dangerously massive hemorrhage

The initial hematocrit may be normal or elevated in spite of considerable blood loss since hemorrhage occurs at the expense of both the plasma and red blood cells The magnitude of the hemorrhage may not become evident for the first 12 to 24 hr depending upon the state of hydration and the rapidity with which the total blood volume is restored by dilution Blood volume measurements with radioactive chromium radioactive phosphorus or Evans blue dye indicate that 40 to 50 per cent of the total red cell mass may be lost without an initial parallel fall in the hematocrit

Leukocytosis as a reflection of hemorrhage is common An increase in the blood urea nitrogen (to levels of 30 to 50 mg per 100 ml) occurs within the first 24 to 48 hr resulting from (1) alimentary absorption of proteins from the digested blood (2) decrease in renal function as the result of shock and dehydration or (3) hypochloremic alkalosis from vomiting or ingestion of soluble alkalies The blood urea nitrogen is often a good index of the extent of the hemorrhage Fever is sometimes observed between the second and fifth day if a large amount of blood remains in the intestinal tract Digestion of blood in the gastrointestinal tract may elevate the blood ammonia level in the presence of extensive liver disease

Diagnosis Peptic ulcer is the most common cause of hemorrhage from the upper gastrointestinal tract

and should be considered first in spite of the absence of pain or an antecedent history Although previous episodes of hematemesis melena or ulcer pain are common silent bleeding with no antecedent ulcer distress occurs in 25 per cent of patients Acute ulcerations or erosions of the stomach and duodenum which are not seen roentgenographically cause bleeding of undetermined origin in approximately 15 per cent of patients

When the diagnosis is uncertain or the source of bleeding has not been established early roentgenologic examination within 24 to 48 hr of the onset of hemorrhage may be indicated if the patient is not in shock or bleeding massively Gastroscopic examination may be helpful in visualizing bleeding erosions and ulcerations which are too small to detect by roentgenography

Esophageal varices tumors of the stomach gastric polyps diaphragmatic hernia with localized gastritis gastritic ulcerations gastritis and blood dyscrasias are considered in the differential diagnosis

The string test may be valuable in determining the site of bleeding in patients with melena of obscure origin The patient is instructed to swallow a marked string which upon withdrawal several hours later is tested for blood or bile The site of bleeding may then be determined by measuring its position on the string in relation to the cardia and duodenum The cardia is approximately 16 in from the teeth the duodenum is designated by the bile stains Blood may also be demonstrated in the gastric contents obtained by gastric intubation

Laboratory aids in addition to the blood studies and blood urea nitrogen determination are the benzidine dihydrochloride test for blood and the uropepsin excretion which is invariably high in massive hemorrhage from peptic ulcer

Medical Management of Massive Hemorrhage *General Principles* Medical management of massive bleeding from peptic ulcer is based upon the (1) replacement of blood loss and treatment of shock (2) acid neutralization and maintenance of nutrition (3) reduction of the motor and secretory activity of the stomach and (4) supportive therapy

The patient should be seen at frequent intervals by a medical surgical team to evaluate the course of the hemorrhage The pulse rate and blood pressure reflect the rate and severity of the bleeding and should be determined at 30 to 60 min intervals in the acute bleeding phase

Replacement of Blood Loss and Treatment of Shock The treatment of shock consists of elevation of the foot of the bed the administration of mild sedation parenterally (such as sodium phenobarbital) and blood transfusions Blood transfusions are indicated whenever the (1) pulse rate exceeds 120 per minute or is rising (2) the blood pressure falls below 90 to 100 mm Hg or (3) evidence of shock is present Approximately 75 per cent of the estimated blood volume should be restored and the hematocrit maintained at 28 to 30 or above by repeated transfusions

Acid Neutralization and Maintenance of Nutrition Warm milk and cream in equal parts or whole milk in amounts varying from 30 to 120 cc as tolerated is administered hourly from 7 00 A M to 10 00 P M and at 2 hr intervals throughout the night as 200 to 250 cc feedings (Table 126 Ulcer Diet I) This supplies the patient with 2400 to 2800 cal and 60 to 70 Gm of protein daily Antacids are administered with the milk-and-cream feedings throughout the day and night Night feedings are necessitated by the marked increase in nocturnal gastric secretion An initial period of starvation with continuous gastric aspiration may be necessary for 24 to 48 hr if there is persistent nausea and vomiting during which the patient is maintained on parenteral fluids Small feedings of warm skimmed milk are then offered and the feedings are gradually increased as tolerated

The hourly regime is maintained for approximately 4 to 6 days until all evidence of active bleeding has disappeared The usual routine ulcer management is then instituted with an Ulcer Diet II (Table 126) supplementary small interval feedings and antacids Gastric aspiration roentgenography and gastroscopy may be performed safely at this time to determine the site and nature of the lesion

Small doses of sodium phenobarbital (0 03 to 0 06 Gm) and atropine (0 0006 Gm) are administered parenterally every 6 hr to reduce the motor and secretory activity of the stomach

Supportive therapy consists in the empirical administration of vitamins parenterally and the proper control of electrolyte and fluid balance Favorable results from the use of buffered solutions of thrombin or powdered Gelfoam have been reported but the substances are not in general use

Constipation and fecal impaction may be prevented by the proper use of cathartics and enemas Cold liquids morphine and aspirin should be avoided since they cause gastric irritation nausea vomiting and spasm

Surgical Treatment *Emergency Surgery* Every effort is made to terminate the bleeding by conservative means and to avoid delay of emergency surgery in those who will not respond to medical management The mortality rate of conservative treatment (2 to 5 per cent) is significantly lower than that of surgery performed during the active phase of bleeding (8 to 15 per cent)

Emergency surgery is indicated when the pulse

blood pressure or hematocrit cannot be maintained by the free use of blood transfusions (500 ml or more every 8 hr) and when bleeding recurs several days after recovery from a hemorrhage

The ulcer is removed surgically if possible When this is not technically feasible the ulcer bed is transfixed with ligatures or the branches of the gastroduodenal artery leading to the ulcer are ligated Subtotal gastric resection is then performed

Elective Surgery Elective surgery is indicated when the patient has suffered two or more hemorrhages while on satisfactory medical management or refuses to follow a medical ulcer regimen The procedure of choice is then subtotal gastric resection

Obstruction

Obstruction to the passage of food from the stomach may be caused by spasm edema inflammation or cicatricial stenosis resulting from an ulcer in the antrum pylorus or duodenum In some instances gastritis or hypertrophic pyloric stenosis may be contributing factors

Symptoms The clinical manifestations of duodenal obstruction include a feeling of fullness or nausea after meals followed by voluntary restriction of food and finally by vomiting There may be no pain or the ulcer pain may become severe and intractable to food or alkalies because of the retention of large amounts of highly acid gastric juice The vomiting may be minimal because of considerable decompensation and dilatation of the stomach

Diagnosis The diagnosis is best established by gastric aspiration and roentgenologic examination The degree and type of obstruction are ascertained by aspirating the stomach nightly (10 P M) after a 4 hr fasting period following the evening meal (6 to 10 P M) and measuring the volume of gastric content obtained Normally not more than 100 ml is present Retention of 150 to 400 ml usually signifies edema or spasm aspiration of 500 to 1 000 ml or more suggests cicatricial stenosis If the nightly retention of gastric juice gradually falls to normal after 7 to 10 days of medical management spasm or edema is likely In the presence of cicatricial stenosis high levels of gastric retention persist

Delay in stomach emptying may be demonstrated on physical examination by a succussion splash or by large gastric peristaltic waves moving from the left rib margin towards the right midabdomen

The roentgenologic examination gives the most accurate evidence of obstruction The site nature and extent of the obstructing lesion may be determined and the degree of retention and stenosis evaluated by measuring the channel fluoroscopically The lumen of the normal duodenal bulb has a diameter of 2 cm patients with marked cicatricial stenosis may present a channel of 2 to 4 mm or less Cicatricial stenosis is often accompanied by dilatation of the stomach and hyperperistalsis

Treatment The treatment depends upon the type and degree of obstruction If the obstruction is mild and edema or spasm is suspected nightly aspirations are not only helpful in evaluating the degree and persistence of the obstruction but constitute good therapy by removal of highly acid gastric juice Medical management alone is usually satisfactory if the obstruction has been caused by edema or spasm The patient may be maintained on an Ulcer Diet I or II (Table 126) with frequent soft feedings and antacids Surgery is necessary when gastric retention and obstruction persist after 7 to 10 days of medical treatment or when the fluoroscopic examination reveals cicatricial stenosis with a narrowed lumen

When the obstruction is marked decompression of the stomach by continuous gastric aspiration for several days is advisable Small liquid or semisolid feedings with discontinuation of suction for 2 hr or more after each feeding may then be attempted Replacement of chlorides and potassium is essential to prevent hypochloremic alkalosis during periods of gastric aspiration or vomiting Alimentation may be administered intravenously with the aim of correcting dehydration acid base imbalance and hypoproteinemia

Subtotal gastric resection is the procedure of choice for cicatricial obstruction but it should not be performed until the stomach has been adequately decompressed and the acid base balance corrected In some instances a posterior gastroenterostomy is preferable particularly in elderly patients who are not good surgical risks This procedure may be combined with vagotomy

Gastrojejunal Ulcer

A marginal peptic ulcer may develop at or near the site of anastomosis of the stomach and jejunum as a complication of gastroenterostomy or gastric resection and is usually seen on the jejunal side of the anastomosis

Incidence Gastrojejunal ulcer is seen more frequently after gastroenterostomy than following subtotal resection It is a rare complication of resection for gastric ulcer and practically never occurs after gastric resection for cancer

Symptoms Pain is the outstanding symptom It is ulcerlike in nature and is usually referred to the left midabdomen and periumbilical area Massive hemorrhage occurs frequently and may be the presenting symptom Chronic perforation into the colon producing a gastrojejunocolic fistula is not uncommon Acute perforation is rare

Diagnosis Recurrent atypical ulcerlike distress following an anastomotic procedure suggests the diagnosis The ulcer may be demonstrated roentgenologically or gastroscopically Failure to visualize the lesion does not exclude the diagnosis however

Treatment Intensive ulcer management should be instituted although surgery is often necessary When a marginal ulcer appears after a gastroenterostomy the gastroenterostomy may be undone and an adequate subtotal gastric resection performed In some instances a vagotomy alone is performed or the vagotomy may be combined with gastric resection The treatment of gastrojejunal ulcer developing after gastric resection is difficult This is the prime indication for vagectomy A higher and more adequate resection may be indicated in some instances

Gastrojejunocolic Fistula

This complication results from perforation of a marginal ulcer into the colon permitting food to pass directly from the stomach into the large intestine The symptoms are those of diarrhea containing undigested food belching of gas with a fecal odor loss of weight dehydration anemia and hypoproteinemia The diagnosis is made by observing the passage of barium directly from the stomach into the colon or from the colon into the stomach during a barium enema Treatment consists of surgical repair after the nutritional and electrolytic state of the patient has been improved or corrected

Postgastrectomy Syndrome

When the reservoir function of the stomach has been removed following a total or subtotal gastric resection the ingested food may enter the jejunum rapidly giving rise to a symptom complex called the *dumping syndrome* This complication may also be seen less frequently after a gastroenterostomy The symptoms consist of one or more of the following a feeling of faintness warmth weakness sweating vertigo palpitation nausea vomiting cramping abdominal or epigastric pain diarrhea and in some instances collapse The complaints may be extremely mild and barely discernible or they may completely incapacitate the patient persisting for weeks or years after the operation

The intrajejunal administration of hypertonic solutions may reproduce the symptomatology of the dumping syndrome Coincident with this are an acute decrease in the circulating blood volume resulting from the shift of plasma water into the intestinal lumen and electrocardiographic alterations attributed to sympathetic stimulation or changes in electrolyte balance Other contributing factors in the dumping syndrome may be (1) distention of the jejunum caused by fluid pouring into the lumen in response to the osmotic properties of the food (2) rapid changes in the blood sugar levels (3) vagal sympathetic imbalance (4) adrenal stimulation

Weight loss (or the inability to obtain the preoperative weight) is one of the most serious manifestations of the postgastrectomy syndrome and may be accompanied by anemia or a spruelike picture with diarrhea or steatorrhea The severity of these symptoms is related to the amount of stomach resected An iron deficiency has been demonstrated after partial gastrectomy and a vitamin B_1 deficiency after total gastrectomy

Treatment consists of (1) frequent feedings (2) a high protein high fat low carbohydrate diet (3) omission of fluids from meals (4) antispasmodics and (5) rest after meals Recently intravenous iron therapy has been recommended Injections of vitamin B_1 may also be helpful after total gastrectomy If marked weight loss persists in spite of dietary and medical management reoperation may be necessary in an effort to restore normal continuity

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246 DISEASES OF THE DUODENUM AND SMALL INTESTINE

Thomas E Machella

DUODENITIS

The term *duodenitis* is applied to an inflammation of the mucosa of the bulbar region of the duodenum Such inflammation may be confined to this area or may be associated with a gastritis especially of the antrum It occurs in individuals subjected to emotional disturbances of the type encountered in peptic ulcer and in chronic superficial and hypertrophic gastritis The symptoms may be somewhat suggestive of a duodenal ulcer Massive hemorrhage may occur Gastric acidity is frequently increased The diagnosis is based on the demonstration of spasm and irritability of the duodenal cap on fluoroscopic examination on the presence of a coarse mottled appearance of its mucosa on the films and on the failure to demonstrate an ulcer crater When an ulcer type of pain is present in patients with such roentgen findings even though some of its features may be atypical an ulcer crater is not infrequently demonstrated at laparotomy or necropsy The treatment of duodenitis is similar to that of peptic ulcer

DUODENAL STASIS AND SPASM

Duodenal stasis and spasm most commonly occur as a result of disturbances in the motor function of the proximal duodenum in emotionally disturbed individuals In the usual case of duodenal stasis a to-and fro swaying of barium in the descending limb of the duodenum associated with delayed gastric emptying is observed during fluoroscopy The barium does not readily enter the transverse duodenum and occasionally refluxes into the stomach In more advanced cases the portion of the duodenum proximal to the vertebral column is greatly dilated and retentive Such an appearance is frequently ascribed to compression of the transverse duodenum by the mesenteric vessels It may be encountered in patients with disseminated lupus erythematosus In duodenal spasm the descending limb fails to fill out during the passage of barium and is visualized as a thin narrowed segment on the films

Symptoms first appear following the onset of an emotional disturbance They consist of a sense of epigastric fullness distention or pain belching anorexia nausea vomiting and headache Loss of weight may be considerable in those with marked stasis The pain which may be severe and colicky is likely to be precipitated or aggravated by ingestion of food and is often relieved by vomiting In duodenal spasm the pain may radiate around to the right costal margin and suggest biliary tract colic

The most important aspect of management in both duodenal stasis and spasm is the discovery and successful handling of the responsible psychogenic factors In the management of duodenal stasis the diet should consist of bland foods of high caloric content The feedings should be small and administered frequently Changes in posture such as lying on one side or the other for an hour after meals or assuming a prone position may relieve postprandial epigastric distress and facilitate emptying of the stomach and duodenum A cholinergic drug such as Urecholine administered preferably by injection will usually prevent the development of stasis if administered before meals or dispel it if given after At times a period of intravenous or intrajejunal alimentation may be required A short circuiting operation such as an enteroenterostomy invariably fails to afford relief unless the underlying psychogenic factors are meanwhile eliminated or an actual mechanical obstruction is present In the management of spasm of the descending limb as a result of either a motor disturbance or a duodenitis a similar dietary and psychotherapeutic regimen together with regular doses of phenobarbital and an effective antispasmodic should be prescribed

REGIONAL ENTERITIS

Regional enteritis occurs in both sexes and at any age The majority of patients are in the third and fourth decades when the diagnosis is first established The disease may be encountered in at least three clinical forms (1) during the first acute episode (2) after one relapse or more and (3) as a chronic affliction not infrequently complicated by obstruction or by abscess or fistula formation Though a lack of uniformity of opinion regarding the etiology of the disease exists accumulating clinical evidence strongly suggests that it is a psychosomatic disorder Emotionally the patients are and have been frustrated for one reason or another Unsatisfactory patient parent relationships often exist Emotional storms and upheavals precede the onset of the disease and the occurrence of relapses Most of the patients are very intelligent and are less dependent and more mentally mature than those with ulcerative colitis

Pathology The disease may be confined to the terminal ileum but may also involve additional segments or all of the mesenteric small intestine and at times the duodenum and/or the cecum and ascending colon In a small proportion of cases in

volvement of the terminal ileum is not demonstrable on roentgen examination or by gross inspection at laparotomy In rare instances the entire small intestine and colon are involved The nature of the pathology depends on the duration of the disease In the acute cases the bowel wall is thickened edematous and hyperemic Occasionally exudate is present on its surface and at times petechiae ecchymoses or small tuberclelike formations The mesentery is usually thickened and its fatty appendages may overlap the bowel The lymph nodes are usually enlarged and firm and varying amounts of free peritoneal fluid may be found In the chronic forms or following repeated relapses the wall of the involved intestine is greatly thickened as a result of edema cellular infiltration and fibrosis Miliary nodules containing epithelial round and giant cells may be found on the serosa Fistulous communications between loops of intestine and other viscera with or without abscess formation may be present

Clinical Picture The presenting symptoms are variable the manifestations may resemble those of acute appendicitis ulcerative colitis intestinal obstruction or a fever whose origin is not readily apparent Occasionally the outstanding manifestation is a massive hemorrhage especially when the jejunum and ileum are involved extensively in an acute process

In the typical acute case or during an acute relapse the symptoms and signs may be somewhat similar to those of acute appendicitis and the diagnosis is established at laparotomy In the chronic form a mild continuous or intermittent diarrhea accompanied by abdominal cramps and distention may be present over a period of months or years Severe diarrhea with bloody stools is more apt to be present when the distal colon is also involved Severe crampy pain in the right lower quadrant may be experienced when the terminal ileum is greatly stenosed particularly at the site of its junction with the colon Visible peristalsis may be detected when obstruction has occurred in such cases constipation and abdominal distention rather than diarrhea are complained of Fever is frequently but not always present It is intermittent in type and not always associated with diarrhea The fever is higher and more persistent when large areas of the small intestine are involved Anorexia nausea and vomiting may occur on a reflex basis as the result of actual obstruction or because of an associated chronic gastritis Manifestations of tetany on the basis of hypocalcemia are rarely encountered During the later stages of the disease a mass is frequently palpable in the right lower quadrant of the abdomen or elsewhere its shape depending on the number of adherent loops presence or absence of an abscess and fistulas and the location of the involved portions of the intestine Evidence of malnutrition including weight loss hypoproteinemia dependent edema and stigmas of vitamin deficiency may be present Complications include fistula formation abscesses at the site of perforation, intestinal obstruction occasionally arthritis and in the acute forms massive hemorrhage Fistulous communications may exist between loops of small intestine in apposition or between small intestine and the colon (especially the sigmoid) abdominal wall or various portions of the genitourinary tract including the bladder ureters and the uterus and fallopian tubes in females

Laboratory Findings Leukocytosis is usually present when the disease is active otherwise the leukocyte count is normal or even low Hypochromic anemia on a nutritional basis may occur and occasionally a macrocytic anemia The erythrocyte sedimentation rate is usually accelerated and the total circulating eosinophils are frequently reduced in the very ill patients Occult blood is found in the stool frequently and occasionally frank blood The latter is more frequently found when the colon also is involved

Roentgenologic Findings In the early stages of the disease roentgenologic changes may not be demonstrable and the examination of the small intestine may be reported as negative or as revealing an abnormal pattern not characteristic of any disease In more advanced stages the involved portion presents a characteristic appearance consisting of greatly narrowed segments of small bowel with dilated areas proximally Evidence of internal fistulas may be present The roentgen appearance of a narrowed terminal ileum is often referred to as the string sign Involvement of the terminal ileum is usually better demonstrated after a barium meal than after a barium enema as a diseased terminal ileum frequently fails to visualize during the latter examination Involvement of various portions of the proximal small intestine may at times be more clearly demonstrated by the small intestinal–enema technique or by the introduction of barium through a Miller Abbott tube into the segment under suspicion Associated involvement of the cecum and ascending colon are best demonstrated by a barium enema

Diagnosis The diagnosis in the acute case is usually made at laparotomy for suspected appendicitis The diagnosis in the chronic variety particularly when the terminal ileum is involved is not difficult when a young person with pain tenderness a mass in the right lower quadrant fever anemia weight loss and the characteristic roentgenologic findings is encountered Not infrequently an appendectomy scar is present A somewhat similar picture may at times be obtained when the

small intestine is involved by Hodgkin's disease primary sarcomatosis primary ileocecal tuberculosis sarcoidosis (Besnier Boeck Schaumann disease) endometriosis and by multiple carcinoids Chronic ulcerative colitis may be differentiated by the character of the stools the sigmoidoscopic picture and the barium enema Hodgkin's disease and primary sarcomatosis of the small intestine run a more severe and progressive course and give rise to rapid emaciation and gross hemorrhage Primary ileocecal tuberculosis is very rare in adults but occasionally occurs in children and adolescents Tuberculous involvement of the ileum is more frequently associated with evidence of tuberculosis elsewhere in the body particularly in the lungs Differentiation from sarcoidosis may not be possible clinically or by roentgenologic means The same applies to multiple carcinoids lymphosarcoma and endometriosis and microscopic examination must be resorted to Sprue usually can be readily differentiated by the clinical picture large frothy and foul smelling stools a macrocytic type of anemia a flat oral glucose tolerance curve and the failure of narrowed segments between dilated areas to persist during the course of the roentgen examination Actinomycosis of the ileocecal region with fistula formation to the external abdominal wall is readily differentiated by finding the characteristic granules in the discharging material

Treatment The type of treatment depends upon the stage and activity of the disease the location and extent of involvement and complications

Conservative management in the absence of obstruction or suppurative complication includes correction of existing deficiencies a high protein low residue diet supplemented with essential vitamins and iron and the discovery and successful handling of the emotional problems underlying the disease If a macrocytic anemia is present folic acid or vitamin B_{12} may be corrective Administration of ACTH or of cortisone has caused dramatic remission of symptoms and signs particularly in patients very ill as a result of toxemia or prolonged fever When cortisone is used it is effective by injection or by mouth and should be administered in large dosage (200 to 300 mg daily) during the first week or two When a favorable response is assured the dosage should be gradually decreased at weekly intervals over a period of 2 to 3 months until a state of good nutrition has been attained Thereafter it is cautiously discontinued In patients with advanced and extensive involvement maintenance therapy may be unavoidable if the patient is to survive When ACTH is used it is administered by intravenous or intramuscular injection in dosages of 20 to 30 mg twice a day for the desired period of time The possibility of an absence of the usual clinical signs of perforation and peritonitis during ACTH or cortisone therapy should be kept in mind After a remission has been induced situations which threaten the patient emotionally should be aborted or prevented so as to avoid relapses

Indications for surgery include intractability obstruction and perforation with abscess and fistula formation When surgery is contemplated the entire small intestine and colon should be re x rayed for detection of skip" areas of involvement if a long interval has elapsed between the initial examination and the decision to resort to surgery In some cases the length of involved intestine contraindicates surgical treatment A sigmoidoscopic examination should also be performed to rule out involvement of rectum and sigmoid Two types of procedure are used depending on the judgment or preference of the surgeon at the time of operation resection of the involved intestine or a short circuiting procedure A high incidence of relapses has followed both procedures usually because not all the diseased bowel wall was removed or short circuited In patients in whom the diagnosis of regional enteritis is made at operation for suspected appendicitis and the diseased segment is not excised it is well to remove the appendix in order to avoid having to consider the possibility of acute appendicitis during subsequent relapses

Prognosis A certain proportion of cases recover from the first acute attack and have no more subsequent symptoms Others experience subsequent relapses at irregular intervals or a chronic progression of the disease Some amazing recoveries have occurred in patients with extensive disease including some in whom the abdomen was explored and closed because the entire small intestine was diseased Death may occur from inanition or from shock and collapse following perforation and peritonitis or from pyemia and septicemia

ACQUIRED DIVERTICULA

Acquired diverticula of the small intestine occur as herniations of mucosa through weak points in the intestinal wall they are examples of pulsion diverticula They are encountered more frequently in the upper small intestine and less frequently as the terminal ileum is approached They are usually single and when multiple often occur in association with diverticula elsewhere in the intestinal tract Most of them are found in individuals beyond the age of fifty years

Uncomplicated acquired diverticula of the small intestine cause no symptoms as a rule The failure to empty properly may result in inflammation and give rise to symptoms including pain nausea vomiting and tenderness Perforation or hemorrhage may occur The sac may become strangulated and gangrenous and at times may be responsible

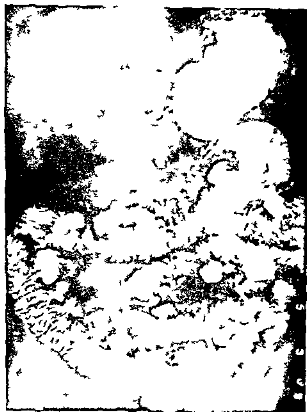


FIG 180 Roentgenologic appearance of the jejunum following ingestion of barium meal The barium filled sacs projecting from the intestine are asymptomatic diverticula

for partial intestinal obstruction Rarely a malignant tumor is found in a large diverticulum of the duodenum The diagnosis is made by roentgenologic visualization of the gut (Fig 180) As a rule no treatment is necessary Complications such as inflammation hemorrhage obstruction perforation or the presence of a tumor require appropriate medical or surgical measures

MECKEL S DIVERTICULUM

Meckel s diverticulum occurs as a result of incomplete obliteration of the omphalomesenteric duct, its structure depending on the degree of obliteration Its length varies from 25 to 125 mm The diverticulum is usually situated on the antimesenteric border of the ileum 25 to 100 cm above the ileocecal valve The lumen is lined with ileal mucosa but heterotopic tissue such as pancreatic cell rests or gastric colonic or duodenal mucosa may also be present The uncomplicated diverticulum usually is asymptomatic Complications include acute inflammation perforation intestinal obstruction volvulus intussusception peptic ulceration when heterotopic gastric mucosa is present and gross hemorrhage Benign and malignant tumors may originate in the diverticulum The roentgenologic demonstration of a Meckel s diverticulum is extremely difficult Most cases are first recognized at laparotomy performed for a suspected acute appendicitis or some other complication

TUMORS OF THE SMALL INTESTINE

All three types of tumor—carcinoma sarcoma and benign lesions—occur in the small intestine though rarely Malignant tumors may reach considerable size are usually single and spread by lymphatic metastasis or direct invasion Benign growths are often polypoid sometimes multiple and usually but not always smaller than malignant tumors

The most common location of carcinoma is the second portion of the duodenum and the next most frequent is the lower ileum Adenocarcinoma occurs more frequently in the duodenum while the scirrhous or "napkin ring" type of carcinoma is more often found in the lower ileum Bleeding gross or microscopic is the most important clinical manifestation The presenting symptoms may also be those of mechanical obstruction and rarely of perforation Metastasis occurs early and recurrence within a few months after resection is the rule

The most common sites of sarcoma are the terminal ileum and jejunum Pain is a frequent symptom The tumors tend to grow externally and are less apt to ulcerate so that bleeding usually does not occur Mechanical obstruction may occur as a result of either distortion of the lumen or infiltration of the bowel wall Ascites may develop as a result of mesenteric or peritoneal involvement or of pressure on the main venous trunks

The most frequent sites of benign tumor are the ileum and the duodenum Adenomas are the most common and myomas are next in frequency with fibromas and lipomas slightly less prevalent About one half these tumors give rise to symptoms as a result of hemorrhage obstruction or intussusception

The discovery of all three types of lesions is made by roentgenologic means Often special intubation procedures may be required The exact type of lesion is determined by microscopic examination after surgical resection

CARCINOID (Argentaffinoma)

Carcinoid is a relatively rare tumor It is found most frequently in the appendix and terminal ileum but may be encountered anywhere in the gastrointestinal tract between the stomach and rectum It arises from chromaffin cells and is a potentially malignant tumor Metastases may occur to the regional nodes peritoneal cavity pancreas liver and bile ducts The tumor as well as its metastases

is capable of liberating serotonin (5-hydroxytrypta mine) a derivative of tryptophan which has a stimulant effect on various smooth muscle systems including the blood vessels gastrointestinal tract bronchi and estrual uterus and may also play a neurohumeral role in the central nervous system The normal blood level of serotonin is 0 2 to 0 4 µg in the presence of carcinoid it may be as high as 4 µg The normal urinary daily output of 5 hydroxyindoleacetic acid the form in which serotonin is eliminated in the urine is 3 to 8 mg while in the presence of carcinoid it may be as high as 350 mg

Carcinoid may cause local manifestations similar to those caused by other tumors of the intestinal tract including intestinal obstruction In addition it may give rise to certain systemic manifestations as a result of the pharmacologic action of the serotonin their nature depending on the susceptibility of the various smooth muscle systems to serotonin as well as to variations in local concentrations of antagonistic compounds These manifestations are usually mild at first but gradually increase in severity over a period of several years as a result of growth and spread of metastases Earliest symptoms include episodes of palpitation stiffness or swelling of face and diarrhea the latter as a result of increased intestinal motility Later spells of tenseness weakness and nausea are complained of Still later the patient experiences episodes of flushing of the skin especially of the face lasting a minute or two attacks of respiratory distress varying from mild dyspnea to wheezing and asthma spells of hot and tingling sensations in the hands and feet transient dysphagia abdominal cramps borborygmi and expulsion of flatus and watery stools In advanced cases attacks of a shocklike picture may develop These consist of weakness abdominal pain extreme cyanosis cold and wet skin and an inability to obtain the blood pressure and pulse Breathing may cease and artificial respiration may be necessary Such syncopal episodes have been precipitated by squeezing a large tumor during physical examination or at laparotomy consequently carcinoid lesions should be palpated gently Other manifestations may include cutaneous telangiectasia injection of the sclerae extreme cyanosis during the flushing episodes eventually leading to a reddish hue of the face with thickening of the skin The latter is not accompanied by polycythemia

The right side of the heart may be involved especially in patients with hepatic metastases The pathologic changes in the endocardium are somewhat similar to those found in the left side of the heart in fetal endocardial fibroelastosis The thickened endocardium consists of spindle shaped fibroblasts located in an edematous stroma but with no elastic tissue and very little collagen Intimal changes may be present in the coronary arterioles similar to those of endarteritis

The prognosis is usually good even in the presence of regional metastases The primary lesion as well as resectable metastases should be excised With resection of the primary lesion the patient may live 10 to 12 years Levels of serotonin in the blood and of 5 hydroxyindoleacetic acid in the urine return to normal after excision of the primary tumor and its metastases It is very likely that compounds capable of neutralizing the effects of serotonin may eventually be developed which will control some of the clinical manifestations

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247 APPENDICITIS

Thomas E Machella

ACUTE APPENDICITIS

Incidence Acute appendicitis can occur at any age but is most often seen between the ages of ten and thirty years It has been estimated that 1 8 per cent of the total population of the United States undergo appendectomy yearly

Etiology The pathogenesis of appendicitis has not been settled to the satisfaction of all Some maintain that the disease is primarily of bacterial origin the bacteria reaching the appendix through its blood supply (hematogenous) or by lodgment in its crypts of swallowed microorganisms (enterogenous) Others maintain that obstruction of the lumen occurs first and that inflammation is secondary The latter is a more likely explanation The anatomic nature of the appendix itself is such that substances which enter it may find difficulty in leaving Though a large variety of mechanical factors can constitute physical handicaps for ready evacuation of the appendix an appendicolith is probably the most important single cause of obstruction of the lumen One or more are found in 50 to 60 per cent of cases of appendicitis Sometimes swallowed foreign bodies such as pins small

bones or lead shot may lodge in the appendix and give rise to obstruction and even perforation of its wall Occasionally worms especially *Enterobius vermicularis* and sometimes *Ascaris lumbricoides* may lodge in the appendix and provoke colic Following obstruction due to any cause the secretory pressure of the appendix produces injury to the tissue with leukocytic invasion pus formation and subsequent gangrene and perforation

The results of bacteriologic examination of the contents of inflamed appendixes vary Undoubtedly the streptococcus plays an important role in the etiology The fact that colon bacilli may rapidly overgrow other organisms may account for the significance sometimes ascribed to their presence Other organisms including anaerobes have been recovered from inflamed appendixes

Clinical Picture The typical attack of appendicitis is characterized by intermittent or colicky pain in the epigastrium or periumbilical region at times generalized but tending shortly after to become localized in the right lower quadrant The onset of the pain is frequently followed by nausea and/or vomiting Anorexia is common it may precede the pain or it may come on with nausea and vomiting Localization of the pain in the right lower quadrant is associated with a change in its character It becomes dull and constant and then gradually increases in severity nausea and vomiting tend to subside Complete obstruction of the lumen is usually associated with pain of a colicky nature The painful episodes are of short duration but recur with increasing severity Cessation of pain may indicate expulsion of an obstructing substance from the appendix into the lumen of the gut but also like the calm before the storm may herald the onset of gangrene and perforation with subsequent peritonitis

In the usual case the temperature rarely exceeds 100 F When gangrene develops it may reach 101 F Perforation and peritonitis are usually associated with still higher temperatures An increased pulse rate is usually present but rarely exceeds 100 per minute unless gangrene or perforation occurs Children are apt to have a higher fever and pulse rate than adults In the latter group both temperature and pulse rate may be normal Constipation occurs in about 15 per cent of the patients during the acute symptoms while diarrhea is less common The incidence of diarrhea in children is difficult to assess as not infrequently laxatives have been administered

The most important physical sign of acute appendicitis is tenderness over the site of the appendix this usually coincides with the region in which the pain localizes The tenderness becomes more diffuse and localization difficult when peritoneal irritation spreads Rebound tenderness may be elicited when the parietal peritoneum is involved in the inflammatory process Rigidity of the abdominal wall may occur as additional evidence of peritoneal irritation Rectal examination with the patient in the left lateral position may elicit tenderness in the right pelvis

Laboratory Findings The leukocyte count is usually elevated the degree of leukocytosis depending on the severity of the inflammation and the presence or absence of suppurative complications It may vary from 10 000 in mild cases to over 20 000 per cubic millimeter when peritonitis is present A normal leukocyte count, however may be encountered even in patients with severe inflammation but in such cases the differential count will usually reveal a marked increase in the number of immature neutrophils as well as an increase in the total number of cells of the myeloid series Children tend to develop a greater leukocytosis than adults

Urinalysis should be performed in all instances of suspected appendicitis and should be especially examined for red blood cells leukocytes bacteria and sugar Barium enema is contraindicated when acute appendicitis is suspected

Complications Peritonitis is a dreaded complication of appendicitis Its presence is usually heralded by an increase in the area of pain tenderness and rigidity and subsequently by abdominal distention and cessation of peristalsis Fever and leukocytosis increase as the process spreads

Perforation of the appendix with extrusion of pus into a pocket formed by adhesions results in an abscess The localization of pain and tenderness which have been diffuse and a lessening of fever and degree of leukocytosis with a restoration of a number of mature neutrophils indicate that the infection has become localized with abscess formation Abdominal palpation may reveal an indefinite tender mass which may also be palpated by rectum When the abscessed wall includes part of the cecum sigmoid renal pelvis urinary bladder, ureter or vagina fistula formation may result A sinus may occur if the content of an appendical abscess finds its way to the skin surface Other complications include suppurative pylephlebitis liver abscess subdiaphragmatic abscess pulmonary embolism adynamic ileus and partial or complete intestinal obstruction as a result of adhesions

Diagnosis The occurrence of epigastric hypogastric or periumbilical pain with subsequent localization in the right lower quadrant associated with nausea and vomiting and tenderness in the right lower quadrant justifies the diagnosis of acute appendicitis Individuals with disease of the spinal cord from any cause when developing acute appendicitis may demonstrate none of the clinical manifestations to point to the appendix as the cause of illness In the aged in whom the primary

process is sometimes vascular occlusion there is little or no antecedent colic The process remains almost asymptomatic until local or general peritonitis sets in

A careful history must be elicited in cases presenting atypical features as appendicitis can simulate almost any acute disease of the abdomen A retrocecal appendix may give rise to pain in the right flank or costovertebral area Location of the inflamed appendix on the psoas muscle may give rise to pain on the anterior and inner aspects of the thigh when the hip is moved Contact with the ureter may give rise to dysuria or frequency microscopic hematuria and radiation of the pain into the genitalia or inner aspects of the thigh Pain low in the back or in the perineum as well as pain on defecation may occur when the appendix is in contact with the sigmoid Left sided appendicitis in older persons may be mistaken for acute sigmoid diverticulitis

Differential Diagnosis The differential diagnostic possibilities include mesenteric lymphadenitis diverticulitis of the cecum or sigmoid carcinoma of the proximal colon and cecum Meckel s diverticulitis regional enteritis acute gastroenteritis urinary tract disorders such as ureteral calculus pyelitis or hydronephrosis of a low lying kidney an inflamed low lying gallbladder perforated peptic ulcer abdominal pain of diabetic acidosis perforation of the cecum secondary to a local carcinoma or an obstructing lesion in the sigmoid or a ruptured diverticulum pelvic inflammatory disease rupture of a graafian follicle ruptured ectopic pregnancy torsion of a pedunculated uterine fibroid or of a small ovarian or paraovarian cyst or of an ovary with a long attachment abdominal crises of tabes rupture of the deep epigastric artery incarcerated inguinal or femoral hernia sequelae of abdominal trauma orchitis in an undescended testis mesenteric occlusion acute porphyria intestinal obstruction abdominal vein phlebitis abdominal colic of plumbism and polyarteritis nodosa

In the final analysis a great variety of extra appendical diseases and lesions may mimic the signs and symptoms of acute appendicitis The mortality of delay is so great as compared to the mortality of a simple appendectomy that one is justified in resorting to laparotomy when there is any reasonable doubt as to the diagnosis Time has not altered the old adage a live patient without an appendix is much better off than a dead person with one

Treatment The treatment of the acutely diseased appendix consists of its removal as soon as the diagnosis is suspected and the patient adequately prepared The time at which surgery should be performed in the presence of complications of appendicitis is a matter for decision in the individual case The administration of cathartics to patients with suspected appendicitis is contraindicated

"CHRONIC" APPENDICITIS OR APPENDICLAUSIS

The term *chronic appendicitis* has been loosely employed to indicate two different entities One is recurrent acute appendicitis which has already been discussed except for the feature of recurrence The other use of the term chronic appendicitis is largely incorrect it has been applied to unexplained persistent symptoms referable to the right lower quadrant resulting from almost any cause but usually due to an irritable cecum secondary to emotional disturbances Patients in the latter category are often made worse by removal of the appendix and are rarely relieved except for psychotherapeutic effect In the absence of clear evidence pointing toward an acute attack operation for *chronic* appendicitis is unjustified

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248 DISEASES OF THE COLON AND RECTUM

Seymour J Gray

The diagnostic approach to the patient with colonic and rectal disease is predicated upon the integration of a careful history and physical examination with properly selected laboratory procedures proctosigmoidoscopy and roentgenography

Symptoms such as constipation diarrhea change in bowel habit rectal bleeding abdominal pain nausea vomiting and weight loss are of particular diagnostic significance The frequency and character of the evacuations and the presence of gross blood melena mucus or pus in the stools deserve

bones or lead shot may lodge in the appendix and give rise to obstruction and even perforation of its wall Occasionally worms especially *Enterobius vermicularis* and sometimes *Ascaris lumbricoides* may lodge in the appendix and provoke colic Following obstruction due to any cause the secretory pressure of the appendix produces injury to the tissue with leukocytic invasion pus formation and subsequent gangrene and perforation

The results of bacteriologic examination of the contents of inflamed appendixes vary Undoubtedly the streptococcus plays an important role in the etiology The fact that colon bacilli may rapidly overgrow other organisms may account for the significance sometimes ascribed to their presence Other organisms including anaerobes have been recovered from inflamed appendixes

Clinical Picture The typical attack of appendicitis is characterized by intermittent or colicky pain in the epigastrium or periumbilical region at times generalized but tending shortly after to become localized in the right lower quadrant The onset of the pain is frequently followed by nausea and/or vomiting Anorexia is common it may precede the pain or it may come on with nausea and vomiting Localization of the pain in the right lower quadrant is associated with a change in its character It becomes dull and constant and then gradually increases in severity nausea and vomiting tend to subside Complete obstruction of the lumen is usually associated with pain of a colicky nature The painful episodes are of short duration but recur with increasing severity Cessation of pain may indicate expulsion of an obstructing substance from the appendix into the lumen of the gut but also like the calm before the storm may herald the onset of gangrene and perforation with subsequent peritonitis

In the usual case the temperature rarely exceeds 100 F When gangrene develops it may reach 101 F Perforation and peritonitis are usually associated with still higher temperatures An increased pulse rate is usually present but rarely exceeds 100 per minute unless gangrene or perforation occurs Children are apt to have a higher fever and pulse rate than adults In the latter group both temperature and pulse rate may be normal Constipation occurs in about 15 per cent of the patients during the acute symptoms while diarrhea is less common The incidence of diarrhea in children is difficult to assess as not infrequently laxatives have been administered

The most important physical sign of acute appendicitis is tenderness over the site of the appendix this usually coincides with the region in which the pain localizes The tenderness becomes more diffuse and localization difficult when peritoneal irritation spreads Rebound tenderness may be elicited when the parietal peritoneum is involved in the inflammatory process Rigidity of the abdominal wall may occur as additional evidence of peritoneal irritation Rectal examination with the patient in the left lateral position may elicit tenderness in the right pelvis

Laboratory Findings The leukocyte count is usually elevated the degree of leukocytosis depending on the severity of the inflammation and the presence or absence of suppurative complications It may vary from 10 000 in mild cases to over 20 000 per cubic millimeter when peritonitis is present A normal leukocyte count however may be encountered even in patients with severe inflammation but in such cases the differential count will usually reveal a marked increase in the number of immature neutrophils as well as an increase in the total number of cells of the myeloid series Children tend to develop a greater leukocytosis than adults

Urinalysis should be performed in all instances of suspected appendicitis and should be especially examined for red blood cells leukocytes bacteria and sugar Barium enema is contraindicated when acute appendicitis is suspected

Complications Peritonitis is a dreaded complication of appendicitis Its presence is usually heralded by an increase in the area of pain tenderness and rigidity and subsequently by abdominal distention and cessation of peristalsis Fever and leukocytosis increase as the process spreads

Perforation of the appendix with extrusion of pus into a pocket formed by adhesions results in an abscess The localization of pain and tenderness which have been diffuse and a lessening of fever and degree of leukocytosis with a restoration of a number of mature neutrophils indicate that the infection has become localized with abscess formation Abdominal palpation may reveal an indefinite tender mass which may also be palpated by rectum When the abscessed wall includes part of the cecum sigmoid renal pelvis urinary bladder ureter or vagina fistula formation may result A sinus may occur if the content of an appendical abscess finds its way to the skin surface Other complications include suppurative pylephlebitis liver abscess subdiaphragmatic abscess pulmonary embolism adynamic ileus and partial or complete intestinal obstruction as a result of adhesions

Diagnosis The occurrence of epigastric hypogastric or periumbilical pain with subsequent localization in the right lower quadrant associated with nausea and vomiting and tenderness in the right lower quadrant justifies the diagnosis of acute appendicitis Individuals with disease of the spinal cord from any cause when developing acute appendicitis may demonstrate none of the clinical manifestations to point to the appendix as the cause of illness In the aged in whom the primary

spective high pressure" emotionally labile individuals Other contributing factors are laxative abuse irritating enemas tobacco excess and coarse food Ice cold or hot liquids may activate the gastrocolic reflex in susceptible individuals and invoke mass peristalsis colonic spasm or diarrhea The irritable colon is often seen as a residual following food poisoning or specific dysentery infections Food allergy is rarely involved

Pathologic Physiology The motor and secretory activities of the colon are controlled by the autonomic nervous system The gastrocolic reflex mediated through the vagus nerve plays a significant role in initiating mass peristalsis Increased parasympathetic activity accelerates the motor and secretory responses while overbalance of the sympathetic system inhibits the activity of the colon Normally a fine balance between the two systems permits the orderly progression of intestinal contents and gas through the intestinal tract without sensory perception or distress

As a result of autonomic imbalance in the emotionally disturbed patient the motor secretory and vascular responses of the colon are no longer properly integrated and provoke a multitude of gastrointestinal complaints

The principal functions of the colon are (1) absorption of water and electrolytes with dehydration of the fecal contents and (2) formation of a reservoir for the colonic contents to permit orderly evacuation

Constipation results from decreased intestinal motility colonic spasm and increased water absorption *Diarrhea* is caused by hypermotility of the colon and a reduced absorption of water resulting in the rapid transit of the liquid colonic contents Intermittent periods of hypomotility and hypermotility are reflected by *alternating constipation and diarrhea*

Distention of the bowel with gas and colonic spasm produce *abdominal pain* An increased secretion of *mucus in the stools* may be a manifestation of emotional disturbances or of chemical bacterial or mechanical irritation

Abdominal distention and rumbling and gurgling of the bowel are produced by excessive gas hyperperistalsis and hypertonicity Increased gas is caused by (1) excessive swallowing of air (2) abnormal fermentation of carbohydrates (3) interference with the intestinal absorption of gases (4) constipation hypomotility or spasm (5) interference with digestion of certain high carbohydrate foods rich in cellulose and (6) interference with the venous circulation Flatus consists mainly of nitrogen in addition to carbon dioxide oxygen and methane

Symptoms The symptoms of the irritable colon vary considerably depending upon which of the previously discussed disturbed physiologic mechanisms is dominant The most common manifestations are abdominal distress distention constipation diarrhea excess mucus secretion and neurocirculatory instability One symptom may replace another as exemplified by alternating constipation and diarrhea

Abdominal distress the most frequent complaint may consist of (1) a sensation of abdominal fullness and discomfort (2) severe regularly recurring cramplike pain (3) a deep dull aching sensation (4) steady intense griping distress or (5) sharp intermittent knifelike jabbing pain It may involve the entire lower abdomen localize in either the right or left lower quadrant or shift from one site to another Often the distress is relieved by defecation or expulsion of flatus Abdominal distention bloating rumbling and gurgling and the frequent passage of flatus are common symptoms and may be associated with anorexia nausea and excess belching

Constipation one of the major complaints is characterized by infrequent evacuations the expulsion of hard dry small pellets or the passage of long narrow ribbonlike or pencil shaped stools resulting from spasm

Diarrhea occurs in approximately 25 per cent of patients The stools are mushy or semisolid and are passed two or more times daily frequently after meals often with urgency or tenesmus *Excess mucus* may be present but there is no blood loss weight loss or nutritional disturbance

Neurocirculatory or vasomotor instability is manifested by weakness fatigue headaches palpitation faintness excess perspiration hot and cold sensations nausea or "nervousness"

Physical Examination Physical examination usually reveals a well nourished patient with no significant abnormalities The colon may be palpable and tender particularly along the descending colon and sigmoid where a narrow tender sausage shaped mass may be present The abdomen is often tympanitic Findings on rectal examination are usually normal

Diagnosis A wide variety of organic diseases may simulate the irritable colon syndrome because of the broad spectrum and variability of its symptoms The diagnosis can be made only after exclusion of other organic diseases by roentgenography sigmoidoscopy and stool examinations for blood ova parasites and bacterial pathogens The diagnosis of irritable colon is suggested by a long history of intermittent attacks of lower abdominal discomfort associated with constipation diarrhea or the passage of excess mucus in the stools without pus or blood Precipitation of the symptoms by emotional factors relief by bowel movements and flatus a long protracted history of laxative

detailed inquiry Emphasis is also placed upon the mode of onset Diarrhea following emotional upheavals chronic cathartic excess dietary indiscretions or the intake of ice cold or hot beverages is often functional in origin In some instances diarrhea may be caused by antibiotics or drugs When nausea vomiting and fever precede or accompany the abrupt onset of diarrhea the most likely diagnoses are food poisoning gastroenteritis or the specific dysenteries Bacterial viral or parasitic infections should be suspected in epidemic or institutional forms of diarrhea Nocturnal diarrhea frequently occurs with ulcerative colitis and diabetic neuropathy

A history of insidious and progressive constipation or alternating constipation and diarrhea with a change in bowel habit should arouse the suspicion of malignancy although these symptoms may also be present in functional disturbances Gross rectal bleeding is characteristically absent in the functional diarrheas and gastroenteritis but may be the presenting symptom of ulcerative colitis the specific dysenteries rectal carcinoma polyps hemorrhoids and intussusception

Approximately *70 per cent of all rectal tumors* are within reach of the index finger No single examination is more valuable and informative than the digital examination of the rectum In some instances combined abdominorectal or rectovaginal examinations are indicated Abdominal palpation often reveals a narrow tender segment of descending colon which may represent a spastic colon ulcerative colitis diverticulitis or feces Repeated examination after the patient evacuates his colon or is given a cleansing enema will aid in excluding "phantom masses" caused by fecal material A persistent mass in the left lower quadrant is suggestive of malignancy diverticulitis or a localized inflammatory process a right side mass is often found with cancer of the right colon regional enteritis granulomatous tumors (amebic or tuberculous) and intussusception

Inspection of the stools is helpful in distinguishing gross bleeding from blood streaking on the surface of the stool usually caused by hemorrhoids Black tarry stools usually signify bleeding from the upper gastrointestinal tract The detection of occult blood by the benzidine dihydrochloride test may offer a useful routine screening procedure for malignancy The presence of persistent occult blood in the stools warrants a careful search for polyps and cancer The cytologic technique for demonstrating tumor cells may be a helpful adjunct Repeated examinations of warm stools for ova parasites and bacterial pathogens are essential in unexplained diarrhea or rectal bleeding

The proctosigmoidoscope and roentgenogram are the most accurate methods (95 per cent) of establishing the diagnosis of colonic and rectal disease The lower 10 to 12 in of the rectum and rectosigmoid areas which are the most difficult to examine roentgenographically are best seen through the proctosigmoidoscope Approximately *70 per cent of cancers of the large bowel* and *90 per cent of rectal and rectosigmoid tumors* can be visualized and diagnosed by this means Indications for the procedure are (1) abdominal complaints in patients over forty particularly where malignancy may be suspected (2) persistent or intermittent diarrhea (3) rectal bleeding or occult blood in the stools (4) unexplained anemia or weight loss (5) symptoms of chronic large bowel obstruction (6) rectal pain (7) presence of a left lower quadrant abdominal mass and (8) as a preliminary to rectal surgery particularly for hemorrhoids or rectal fistulas

Routine proctosigmoidoscopy for all patients over forty years of age as a screening procedure to detect early cancer or precancerous lesions has been advocated particularly since polyps are found in 6 to 8 per cent of all patients sigmoidoscoped routinely The examination is also exceedingly valuable in following the course of ulcerative colitis and other inflammatory processes in obtaining culture material in the parasitic and dysentery diseases and in procuring biopsy material

The roentgen examination is the only satisfactory method for examining the entire colon and is indicated in all patients with colonic symptoms but it should be preceded by a careful history and by a physical and proctosigmoidoscopic examination. The diagnosis of a functional disorder is not tenable until organic disease is excluded by these procedures

IRRITABLE COLON SYNDROME

The irritable colon syndrome may be defined as a symptom complex caused by abnormal irritability or neuromuscular imbalance of the colon sufficiently severe to produce colonic dysfunction and abdominal distress The highly variable clinical expressions of this syndrome have been described as spastic colon unstable colon colonic neurosis mucous colitis cathartic colitis nervous indigestion dyspepsia functional colitis spastic constipation nervous diarrhea or asynergia of the colon, depending upon which phase of altered motor or secretory function predominates The term *colitis* is not justified since there is no known inflammatory or organic component in this syndrome

Etiology Emotional disturbances tensions and life stresses are the most common denominators Colonic dysfunction has been attributed to imbalance of the autonomic nervous system in emotionally unstable tense anxious apprehensive intro

Symptoms Constipation may be accompanied by abdominal discomfort backache general abdominal distention anorexia belching and the passage of flatus At times liquid feces may be passed around the impaction presenting the paradoxical symptoms of diarrhea With excessive straining at stool hemorrhoids mucosal abrasions anal fissures or fistula in ano may develop

Treatment The management of rectal constipation is similar to that of the irritable colon Organic disease should be excluded by physical examination proctosigmoidoscopy and barium enema before instituting therapy Treatment consists of (1) establishment of a definite bowel habit at a time of the day when the patient can relax particularly after breakfast when the most active gastrocolic reflex occurs (2) dietary care as described previously with adequate fruits vegetables and fluids (3) avoidance of routine cathartics and enemas (4) abdominal exercises (5) antispasmodics and (6) reassurance that a daily evacuation is desirable but not essential to good health

If constipation persists during the early period of treatment mild cathartics (milk of magnesia 30 to 60 ml) or enemas of water physiologic saline solution (1 tsp of salt to a quart of water) or oil (60 to 90 ml warm olive oil as a retention enema) every 2 to 4 days may be necessary until spontaneous evacuations appear Glycerin rectal suppositories are often helpful The patient must be constantly reassured that no organic disease exists

Removal of fecal impactions is often necessary in the bedridden patient Ointment or jelly is instilled into the anal canal the anus is dilated with the fingers and the impaction is broken up digitally and removed Approximately 90 to 120 ml warm olive oil is then administered rectally as a retention enema and is followed later by a tap water enema

CONSTIPATION AND DIARRHEA

A further discussion of constipation and diarrhea is presented in Chap 16

NONSPECIFIC ULCERATIVE COLITIS

This form of colitis is characterized by a diffuse ulcerative inflammation of the colon which cannot be ascribed to any known single cause and is manifested by bloody diarrhea often accompanied by generalized systemic symptoms The idiopathic form of ulcerative colitis must be distinguished from ulcerative colitis of specific etiology such as that associated with tuberculosis amebic or bacillary dysentery lymphopathia venereum vitamin deficiency and uremia discussed elsewhere (Chaps 19 123 188 194)

Incidence Among chronic intestinal diseases ulcerative colitis is relatively common and appears to be increasing in frequency It is found equally among men and women and may occur in childhood but is most common in the second third and fourth decades

Etiology and Pathogenesis The cause of nonspecific ulcerative colitis is unknown Various bacteria implicated in the disease have proved to be secondary invaders (alpha and beta streptococci staphylococci diplococci *Bacillus necrophorus*) Viruses allergic factors and nutritional deficiencies do not appear to play significant etiologic roles Bacillary and amebic dysentery are precursors in only a small percentage of patients The irritable colon does not predispose to ulcerative colitis

Lysozyme a mucolytic enzyme has been suggested as a causative agent in view of the high titer found in the stools of patients with this disease It was postulated that lysozyme removed the protective colonic surface mucus favoring ulceration of the denuded mucosa by proteolytic enzymes such as trypsin Lysozyme however does not play a significant role in the pathogenesis of ulcerative colitis It serves as a measure of the activity of the disease and the extent of the inflammatory reaction and is found in considerable amounts in pus and granulation tissue Lysozyme moreover cannot digest or dissolve colonic mucus and various antilysozyme agents particularly detergents which inhibit the enzyme do not alter the course of the disease

Emotional conflicts anxiety and resentment are often associated with exacerbations and recurrences of the disease and are manifested by vascular motor and secretory abnormalities of the colon mediated presumably through the autonomic nervous system There is no conclusive evidence however that a specific personality trait predisposes to the disease or that the disease is exclusively a psychosomatic process

The generalized systemic nature of the disease the associated arthritis and erythema nodosum like lesions the submucosal inflammatory reaction and the changes in the ground substance of the basement membrane of the epithelial cells suggest that nonspecific ulcerative colitis may fall in the group of collagen diseases

Pathology The most striking change is found in the mucosa and submucosa of the colon and rectum The entire lining is often involved in a diffuse severe process of ulceration inflammation and congestion As the disease progresses the mucosa becomes thickened and more diffusely ulcerated Coalescence of the ulcerations may lead to denudation of the mucosal surface resulting in thinning of the bowel and susceptibility to perforation Linear longitudinal ulcers extend along or between the

abuse or the enema habit often characterize the clinical picture

The proctosigmoidoscopic examination is essentially normal or may reveal spasm at the rectosigmoid narrowing of the lumen or excessive mucus secretion Roentgen examination by barium enema is often normal or presents rapid filling of the colon increased segmentation or an accordionlike appearance of the transverse colon A contracted spastic descending colon and sigmoid may appear as a straight narrow tube without haustral markings

Differential Diagnosis Carcinoma of the colon diverticulitis ulcerative colitis regional enteritis the specific dysenteries acute appendicitis carcinoma of the stomach or pancreas duodenal ulcer and gallbladder disease may produce symptoms simulating those of the irritable colon

Treatment Treatment of the patient with an irritable colon involves psychologic rehabilitation dietary care and the use of antispasmodics and mild sedatives

Successful treatment depends upon a close rapport between the physician and patient Situations of conflict and stress occupational difficulties social financial sexual and environmental problems should be discussed freely and related to the presenting complaints The patient is given insight into the mechanisms by which emotional tensions fears anxiety and hostility express themselves The diagnostic procedures are discussed in detail to allay the patient s anxiety concerning organic disease such as cancer and ulcerative colitis Every effort is made to prevent the patient from becoming bowel conscious Intensive psychotherapy is rarely necessary

Dietary management consists of the administration of a bland diet containing liberal amounts of meat fish chicken eggs cheese cooked fruits and cooked vegetables (similar to the Ulcer Diet IV in Table 126 described in Chap 245) Raw fruits raw vegetables and coarse foods are eliminated since they may initiate increased peristaltic activity and spasm "Gassy" foods (high in carbohydrate or cellulose) such as honey candy syrups cabbage cauliflower potatoes coleslaw radishes onions cucumbers tomatoes broccoli squash and turnips are restricted Ice cold or hot liquids which may induce spasm should be avoided Coffee and alcoholic beverages are usually limited

During periods of diarrhea all fruits and vegetables are eliminated and tobacco excess which often stimulates intestinal activity is prohibited The constipated patient is instructed to add two or three servings of both cooked fruits and cooked vegetables to the daily diet including liberal servings of spinach and prunes Adequate water intake is essential Laxatives and enemas should be discontinued and bowel regulation encouraged by establishing a definite time for evacuation In some instances milk of magnesia (15 to 60 ml) is effective as a temporary measure An occasional tap water or oil retention enema may be necessary early in the management to prevent rectal impaction

Antispasmodics are valuable adjuncts in the management of the irritable colon Tincture of belladonna (10 to 15 drops three or four times daily) and atropine (0 3 to 0 6 mg four times daily) are the most satisfactory The clinical superiority of Banthine or Neo banthine over adequate doses of atropine has not yet been proved Phenobarbital (0 15 to 0 03 Gm three or four times daily) and the tranquilizing drugs are also helpful particularly in the anxious patient Morphine should be avoided since it often increases intestinal spasm In instances of severe pain or intractable diarrhea codeine (0 03 to 0 06 Gm) or paregoric (5 to 10 ml) may be used Kaolin bismuth and bulk cathartics are not recommended Vitamin supplements may be necessary

RECTAL CONSTIPATION (*Dyschezia*)

Rectal constipation (simple constipation) results primarily from a failure of the defecation reflex The transport of feces through the colon proceeds at a normal rate until the feces enter the rectum When the defecation reflex is ignored or fails to appear feces accumulate in the rectum and become dehydrated and often impacted

Etiology and Pathogenesis Rectal constipation is one of the most common complaints of civilized man Voluntary inhibition of the defecation reflex is the most frequent cause It is accomplished by forcible contraction of the external anal sphincter and relaxation of the muscles of the anterior abdominal wall aided by thoracic breathing Defecation is thus forcibly avoided until mass peristalsis is completed When segmentation begins again there is further dehydration and reduction in the size of the fecal contents The walls of the rectum become adapted to the fecal contents and the sensation of fullness and distention disappears

Inhibition of the defecation reflex is established early in life as part of the toilet training of the infant and continues throughout life as a result of the exigencies of daily living This disruption of a regular habit pattern is further accentuated by fatigue emotional disturbances and anxiety regarding daily evacuation Pain in the rectum from hemorrhoids or fissures encourages further voluntary inhibition of defecation Other causes are lack of exercise atony of the rectum immobilization in bed and weakness or injury of the pelvic and abdominal muscles resulting from pregnancy or ascites

The small intestine should be examined by a barium meal to detect associated areas of involvement

Differential Diagnosis Warm fresh stools and rectal swabs should be cultured for pathogenic organisms and a careful search made for *Endamoeba histolytica* Amebic ulcers appear as sharply punched out discrete irregular undermined lesions separated by normal mucosa differing from the diffuse granular ulcerated appearance characterizing nonspecific ulcerative colitis *Bacillary dysentery* is distinguished by the demonstration of specific dysentery organisms Proctitis and sigmoiditis of *lymphogranuloma venereum* may be identical proctoscopically with nonspecific ulcerative colitis but lymphopathia venereum is characterized by a history of enlarged inguinal glands predilection for the female the presence of rectal stricture hyperglobulinemia and a positive Frei test Primary *tuberculosis* of the intestinal tract usually involves the cecum and ascending colon and is often associated with pulmonary tuberculosis *Regional enteritis* is less likely to produce gross blood in the stools and presents a characteristic roentgen picture and a normal mucosa on sigmoidoscopic examination *Diverticulitis* of the colon may produce some of the symptoms of ulcerative colitis but is easily distinguished roentgenologically and usually occurs in an older age group *Malignancies* of the colon are differentiated by roentgen and sigmoidoscopic examinations *Uremic colitis* is readily recognized by the accompanying clinical and laboratory evidence of renal failure

Complications Complications include pseudopolyp formation malignant degeneration rectal strictures perforation with localized or generalized peritonitis hemorrhage and perianal or rectal fistulas and abscesses Other complications are acute arthritis erythema nodosum anemia thrombophlebitis or thrombosis of the veins of the extremities hypoproteinemia clubbing of the fingers fatty liver amyloid disease retarded sexual and physical development uveitis amenorrhea and marked electrolyte unbalance

Cancer occurs in 3 to 10 per cent of patients particularly if the ulcerative process remains active for a period of 10 years or longer

Medical Management There is no specific treatment for this disease Emotional and physical rest are essential to the healing of the diffuse inflammatory process Attention to the patient s emotional problems and dietary care are directed toward decreasing gastrointestinal activity Bed rest and hospitalization are usually necessary It is often advisable to restrict visitors and members of the family who may disturb the patient emotionally

Psychotherapy The principles of the psychotherapeutic approach are similar to those discussed under Irritable Colon Syndrome Successful therapy depends in part upon the physician s ability to instill confidence and hope in the anxious resentful frustrated acutely ill patient Every effort should be directed towards rehabilitating the patient and returning him to an active normal life with a minimum of restriction as soon as possible Active psychotherapy during the acute phase often aggravates the disease and is contraindicated Most emotional problems are best handled by the attending physician In selected instances however formal psychiatry may be helpful in the subacute or chronic phase



Fig 181 Acute stage of ulcerative colitis involving the entire colon Note diffuse ulceration and irregular saw-toothed appearance of the rectum sigmoid and entire colon accompanied by shortening narrowing and loss of haustration.

Diet A high calorie high protein bland diet adequate in minerals and vitamins (similar to that prescribed under Irritable Colon Syndrome Treatment) is recommended Fruits and vegetables as well as fruit juices are avoided in the presence of diarrhea Frequent interval feedings containing protein supplements are prescribed Ice cold fluids and tobacco are excluded since they may stimulate intestinal motility The diet is supplemented with vitamins either orally or parenterally particularly vitamin K and vitamin C The patient s weight and calorie intake are followed carefully

tenial muscle landmarks Polypoid hyperplasia and regeneration may be found in some areas The submucosal and muscular layers are inflamed early and subsequently undergo fibrosis and contraction resulting in marked narrowing of the lumen

The inflammatory process in general is exudative and reparative without any granulomatous tendencies It may be nonspecific in origin or arise from the submucosal coalescence of mucosal crypt abscesses or from intestinal infarction caused by a necrotizing vasculitis resembling periarteritis nodosum and thromboangiitis obliterans

The rectum and sigmoid are the most common sites of involvement the descending and transverse colons are next most frequently ulcerated and the cecum least often Extension of the ulcerative process to the ileum may occur in approximately one third of cases Segments of the small intestine may also be involved Ulcerative colitis restricted to the right side of the colon is uncommon Regional enteritis and ulcerative colitis are two distinct morphologically distinguishable diseases

Symptoms The onset of ulcerative colitis may be either sudden or insidious Its course may be slowly progressive chronic and irregular with exacerbations and remissions or rapid and fulminating particularly in younger individuals The disease tends to be chronic and irreversible A few patients are cured permanently if the ulceration is localized to the rectum or sigmoid The remainder are affected intermittently for life

The clinical picture depends upon the site extent and severity of the inflammatory process When the disease is limited to the rectum or rectosigmoid the onset may be gradual and the only presenting symptom is the passage of red blood and mucus in the stool accompanied by constipation or diarrhea The stools at first may be well formed hard and dry As the disease progresses the number of evacuations may reach 15 to 20 or more daily with rectal incontinence of a serous exudate containing red blood pus mucus and gas associated with tenesmus and abdominal cramping pain Fever may persist for days or weeks loss of appetite is common and weight loss extreme Nausea and vomiting occur only occasionally and abdominal distress may be absent in some instances

In the chronic phase the patient passes two to five semisolid or watery stools daily often with gross blood and appears anemic and malnourished Repeated remissions and exacerbations over a period of years may result in chronic disability

In the severe fulminating form the onset is abrupt with continuous loose watery explosive stools containing gross blood gas and mucus accompanied by high fever tachycardia complete anorexia weakness severe anemia and profound debility Death may result from perforation generalized peritonitis massive hemorrhage inanition and severe electrolyte imbalance

Diagnosis The history of frequent liquid evacuations containing blood mucus and pus in a patient whose stools are free of specific pathogens or parasites suggests the diagnosis of nonspecific ulcerative colitis Sigmoidoscope and roentgen examinations establish the diagnosis when the patient can safely undergo these procedures

Since the mucosa of the rectum or rectosigmoid is involved in approximately 90 per cent of patients with ulcerative colitis the diagnosis may be made by proctosigmoidoscopic examination in the vast majority of patients often before an abnormality is discernible by roentgen examination In the severe acute fulminating type sigmoidoscopy and roentgen examination should be deferred until pain fever spasm and irritability have diminished

The examinations must be performed with care Cleansing soapsuds enemas and cathartics as preparation for sigmoidoscopy and roentgen examination are contraindicated because of the danger of perforation or hemorrhage

Sigmoidoscopic Examination The appearance of the rectum and sigmoid depends upon the severity of the disease During the acute phase the rectal mucosa appears edematous and engorged presenting excess mucus and many minute superficial pin point bleeding areas Swabbing with cotton reveals a diffusely granular freely bleeding friable mucosa Visualization of the ulcerations depends upon the degree of mucosal edema Later in the disease the ulcerations and denudation may be extensive and are accompanied by a thick mucopurulent sanguineous exudate In the chronic state the mucosa appears thickened pale firm and granular The lumen may be narrow and the normal mucosal architecture is absent or distorted Pseudopolyps may be seen in the rectum or sigmoid

Roentgen Examination of the Colon The roentgen appearance of the barium enema does not always parallel the severity of the process and may be normal early in the disease when the sigmoidoscopic examination presents the classical appearance of diffuse ulceration The earliest findings are those of a fine irregular serrated or saw toothed appearance of the barium filled segment commonly associated with spasm and irritability (Fig 181) With extensive involvement the normal mucosal pattern is distorted grossly irregular or absent Areas of polypoid hyperplasia appear as circular irregular filling defects As the disease progresses the haustrations disappear and the colon appears shortened and the lumen narrowed giving the classical lead pipe appearance (Fig 182) Involvement of the terminal ileum is indicated by rigidity narrowing or dilatation and distortion of the mucosal pattern

The beneficial effects of steroid therapy and the fall in fecal lysozyme titer may be attributed in part to a decrease in the extensive inflammatory process within the tissue as well as the diminution of the systemic and toxic manifestions

Remissions induced by hormone therapy are not permanent Relapses and reactivation of the disease are seen in 75 to 80 per cent of patients at varying intervals after steroid treatment is discontinued Long term hormone therapy however may effectively sustain patients in a satisfactory remission for prolonged periods of time and is helpful in preventing chronic invalidism

During the acute phase of the disease adrenocorticotropic hormone is administered intravenously in doses of 20 mg daily in 500 ml glucose and water as an 8 hr continuous drip or intramuscularly (20 to 30 mg as the purified gel twice daily) for 7 to 14 days Cortisone may also be useful in inducing a remission and is prescribed intramuscularly (200 to 300 mg daily) or orally (50 to 75 mg four times daily) After 7 to 14 days the dose of hormone may be gradually reduced as clinical improvement becomes evident

Sulfonamides or antibiotics should be administered in conjunction with hormone therapy Gantrisin or sulfadiazine (1 0 Gm four times daily) is adequate in the milder forms of the disease In the presence of sepsis or peritonitis streptomycin and penicillin are preferable Potassium chloride (1 0 Gm orally two to three times daily) is recommended particularly in the acute phase of the disease to compensate for the urinary and fecal loss Blood transfusions vitamins sedatives antispasmodics and antacids are administered as required

Once a satisfactory remission has been induced cortisone may be given orally for prolonged periods of time Patients have been maintained on hormone therapy for 2 years or longer The usual maintenance oral dose of cortisone varies from 75 to 150 mg a day in three divided doses of 25 to 50 mg Long term cortisone therapy is supplemented by oral sulfonamides or antibiotics intermittently potassium chloride vitamins antispasmodics and dietary care

Cortisone therapy should not be terminated abruptly The dose is tapered gradually before discontinuation to prevent adrenal suppression With prolonged hormone therapy it may be advisable to activate the adrenal cortex intermittently at 6 to 9 month intervals by brief periods of adrenocorticotropic hormone stimulation

Perforation and hemorrhage are exceedingly rare complications following steroid therapy Gastrointestinal ulceration does not present a significant problem in this group of patients although a pre existing peptic ulcer should be excluded before instituting long term hormone therapy Antacids and interval feedings may be prescribed to prevent gastric complications Psychic disturbances are encountered rarely if the patient is maintained on small doses of phenobarbital and is under careful surveillance for undue excitement or overstimulation

Surgery Surgical intervention is necessary in 10 to 15 per cent of patients Indications for surgery are (1) rectal stricture (2) perianal fistula and abscess (3) intractable diarrhea anemia and malnutrition (4) recurrent massive hemorrhage (5) pseudopolyposis (6) malignant change and (7) complications such as arthritis and pyoderma gangrenosum Because of the danger of malignant degeneration surgery should be recommended in the presence of long continued persistent activity of the ulcerative process over a period of 10 years or more

Ileostomy with subsequent colectomy is the surgical procedure of choice Recently subtotal or total colectomy in one stage with ileostomy has been recommended Many of these surgical procedures may now be performed as elective rather than emergency procedures as a result of the judicious use of steroid hormones and other supportive measures

Prognosis The over all surgical and medical mortality in ulcerative colitis approximates 10 per cent The disease tends to be chronic and is characterized by frequent exacerbations and remissions Permanent remission after the initial attack is uncommon Satisfactory rehabilitation may be anticipated in 65 to 75 per cent of patients treated by conservative means The disease presents a milder course in older individuals

DIVERTICULOSIS AND DIVERTICULITIS

Diverticula of the colon are abnormal outpouchings or sacculations which may occur throughout the gastrointestinal tract and are most common (80 per cent) in the sigmoid colon (Fig 184) (Meckel s diverticulum is described in Chap 246) Diverticula of the large intestine are found in 5 per cent of individuals over forty years of age increasing in frequency with each decade past middle life Most diverticula are multiple and are of the false variety consisting of mucosa and serosa, presumably acquired in origin although true diverticula containing all the coats of the bowel wall may be found

Diverticulosis usually refers to noninflammatory uncomplicated diverticula When inflammation occurs in one of these pouches (10 to 20 per cent) the term *diverticulitis* is applied Diverticulitis usually involves the sigmoid colon may be acute or chronic and is seen more frequently in men



Fig 182 Chronic stage of ulcerative colitis in a 50 year old woman with a 20 year history Her presenting symptoms were diarrhea and severe blood loss The colon is narrow and tubular presenting a lead pipe appearance with absence of haustration A discrete pseudopolyp revealing epithelial hyperplasia was found in the transverse colon

Supportive Measures The free use of blood transfusions contributes significantly to the medical management Intravenous dextrose solutions protein hydrolysates and the parenteral administration of albumin may be helpful Correction of fluid and electrolyte imbalance (particularly potassium and chloride loss) is essential Tincture of belladonna (10 to 30 drops four times daily) or atropine (0 6 to 1 mg four times daily) is administered to diminish intestinal motility Phenobarbital (0 03 Gm four times daily) is also helpful as a general sedative Codeine (0 03 Gm) or small doses of tincture of opium helps control the diarrhea and abdominal discomfort Bismuth subcarbonate and kaolin are not effective over a prolonged period of time

Sulfonamides and Antibiotics The sulfonamides and antibiotics are not specific for the disease and do not alter its course They may be effective however in decreasing secondary infection and diminishing the total bacterial content of the feces particularly in the acute septic phase of the disease Sulfadiazine and Gantrisin (either one in doses of 1 Gm four to six times daily) are the most satisfactory sulfonamide preparations and are preferable to the nonabsorbable drugs such as Sulfasuxidine since they afford greater penetration through the entire bowel wall A number of other sulfonamide drugs including azopyrin (1 0 Gm six times daily) have been recommended Streptomycin given orally or parenterally has only a transitory effect on the fecal flora therapeutic results with chloramphenicol and Terramycin are not impressive Aureomycin usually aggravates the diarrhea Penicillin may be valuable particularly in the presence of gram positive organisms When perforation of the bowel is suspected a combination of antibiotics such as penicillin and streptomycin may be lifesaving

Hormone Therapy The adrenal steroids are valuable adjuncts in the therapy of ulcerative colitis Hormone therapy does not constitute a cure but may induce remissions when administered in adequate dosage and properly integrated with the general medical regimen It is particularly indicated (1) in the acute fulminating phase of the disease associated with systemic manifestations (2) during the acute exacerbations in the chronic stage when complications are not present (3) as a preoperative measure in patients requiring ileostomy and (4) as long term maintenance therapy in chronic intractable colitis Steroid therapy is usually not necessary in the mild form of the disease

No significant sustained therapeutic hormonal response may be anticipated in the presence of extensive cicatrization of the colon rectal strictures perianal fistulas abscess formation or perforation with peritonitis although steroid therapy is often valuable in preparing patients with these complications for ileostomy

Following the administration of adrenocorticotropic hormone or cortisone and coincident with the induced remission there is a consistent and prompt fall in the fecal lysozyme titer to levels characteristic of the remission phase (Fig 183)

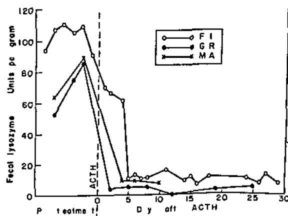


Fig 183 Effect of ACTH upon the fecal lysozyme titer in three patients (F I G R and M A) with ulcerative colitis Note the prompt fall in the fecal lysozyme titer within 5 days following the administration of ACTH accompanying the clinical remission

enth decades although it may be seen in child hood and adolescence

Etiology The polyp is regarded as the most common precursor of colonic and rectal cancer Malignant transformation of single or multiple polyps has been definitely established Regenerating areas of epithelial hyperplasia in chronic ulcerative colitis may also undergo malignant degeneration There is no evidence that diverticulosis parasites constipation or hemorrhoids predispose to cancer A hereditary tendency however probably exists in view of the familial incidence of the disease

Pathology Approximately 75 per cent of all large bowel malignancies involve the left colon The rectum rectosigmoid and sigmoid flexure are the most common sites of colonic involvement (65 to 70 per cent) followed by the cecum and ascending colon descending colon transverse colon hepatic flexure and splenic flexure in order of frequency Multiple primary carcinomas of the colon may occur but are not common (3 to 4 per cent)

The vast majority (95 per cent) of malignancies of the colon are adenocarcinomas the remainder are epitheliomas usually of the squamous cell type involving the anus Sarcomas of the lymphomatous variety and malignant melanomas are rare

Adenocarcinomas of the colon may be divided into four types (1) medullary (2) scirrhous (3) colloid and (4) papillary The ulcerating fungating cellular *nodular* or *medullary* tumor projecting into the lumen or encircling the bowel is the most common In the left colon the small "napkin ring *scirrhous* variety with predominant scar tissue formation produces a firm contracting tumor (Fig 185) Large *colloid* tumors containing mucinous or gelatinous material with little evidence of cellular activity occur in approximately 5 per cent of all malignant tumors and are most common in the cecum and ascending colon *Papillary* carcinomas are usually seen in the left side of the colon

The largest tumors (medullary and colloid) often occur in the cecum and proximal colon Medullary tumors in the distal colon however are usually smaller because of scar tissue contraction and may cause partial obstruction perforation abscess formation or fistulas Carcinomas of the narrower distal colon are often scirrhous and may also produce obstruction by encircling the lumen with cicatricial tissue

Broders classification of malignancy estimates the rapidity of growth and early invasion by dividing tumors into four groups depending upon the degree of cell differentiation The more differentiated and less malignant types of tumor (grades 1 and 2) are found in approximately 75 per cent of carcinomas of the colon Epitheliomas are highly malignant (grade 3) and metastasize early as do sarcomas and melanomas The colloid cancer grows slowly and metastasizes late although regional lymphatic extension is common and widespread

Metastases occur most commonly by way of the lymphatics involving the regional lymph nodes liver and lungs most frequently Colonic tumors also spread by direct extension or through the blood stream Metastases may reach the brain directly through the paravertebral veins

Symptoms Cancer of the colon and rectum presents no characteristic symptoms in the early stages The patient is often completely asymptomatic Vague abdominal distress flatulence and constipation may be discernible but are minimal so that 9 to 12 months usually elapse between the onset of symptoms and the diagnosis The presenting complaint depends upon the site of the lesion the nature and extent of the tumor and complications such as ulceration perforation obstruction or metastasis

The symptoms of the left and right halves of the colon may be indistinguishable or may differ considerably depending upon the stage of the disease and the type of tumor In the left half of the colon the symptoms are usually obstructive in nature since the tumors are constricting in type the fecal contents are more solid and the lumen narrower (Fig 185) Carcinoma of the right half of the colon rarely causes obstruction because the fecal stream is liquid the tumors are softer and the diameter of the colon is larger Tumors in this area are more likely to produce (1) vague abdominal distress (2) anemia or weakness and (3) an abdominal mass The transverse colon is an area of transition in which the colonic contents change from liquid to semisolid Consequently tumors in this area present symptoms of either the right or left colon or both

Carcinoma of the Left Half of the Colon The predominating symptoms are those of *obstruction* resulting from encroachment upon the lumen of the bowel The earliest warning may be a change in bowel habit which in itself is not pathognomonic but is usually sufficiently significant to warrant suspicion of malignancy Other early symptoms simulating those of the irritable colon are constipation diarrhea flatulence and abdominal distress As the obstruction progresses cramping or colicky abdominal pain borborygmi and distention ensue Progressive constipation or obstipation is common Gross blood in the stool may appear in the advanced stage but anemia is not so common nor so severe as in carcinoma of the right colon Weight loss is a late sign

Lesions of the rectum may produce increasing constipation diarrhea rectal pain or a feeling of



FIG 184 Roentgenologic appearance of colon following subsidence of an attack of acute diverticulitis Several diverticula are present in the sigmoid Site of involvement is indicated by arrows

Etiology The cause of diverticula formation is unknown An inherent weakness at the point at which the blood vessels pierce the intestinal wall has been implicated Excess fat may be a contributing factor Diverticulosis is alleged to occur in sedentary obese constipated individuals and is seen equally among men and women The high incidence of diverticula in the sigmoid has been attributed to anatomic fixation of this area making it more susceptible to changes in intraluminal pressure

Symptoms Diverticula produce no significant symptoms other than those associated with an irritable colon constipation or inflammation

The symptoms of diverticulitis are caused by inflammation of the diverticula or obstruction of the colon resulting from the inflammatory reaction and scar tissue formation The characteristic symptoms of acute diverticulitis are abdominal pain usually localized to the left lower quadrant accompanied by signs of peritoneal irritation localized muscle spasm fever and leukocytosis Diverticulitis of the sigmoid is frequently referred to as left sided appendicitis Inflamed diverticula in the cecum or ascending colon may simulate acute appendicitis The acute *inflammatory process* may subside or progress to perforation abscess or fistula formation peritonitis or obstruction Constipation or alternating diarrhea and constipation is common Gross bleeding occurs in 10 to 20 per cent of patients Hemorrhage may be massive in rare instances

Obstruction of the colon is caused by edema infection fibrosis or angulation at the site of the diverticulitis Recurrent cramplike abdominal pain in the left lower quadrant tenderness protective muscle spasm and distention produce a clinical picture resembling that of carcinoma of the large bowel Approximately one third of patients develop an inflammatory mass palpable either by abdominal or rectal examination

Diagnosis The diagnosis may be established by the roentgenologic demonstration of diverticula (Fig 184) or a localized ragged saw tooth distortion of the mucosal pattern of the colon The differentiation between carcinoma and obstructive diverticulitis by roentgenologic criteria may be difficult Diverticulitis does not predispose to malignancy although the two conditions may exist coincidentally The problem is not that of diverticulitis developing into carcinoma but the inherent difficulty in the differential diagnosis

Treatment Diverticulosis requires no specific therapy other than correction of constipation and the treatment of the irritable colon A bland diet free of coarse fibers and seeds and mineral oil may be prescribed

Acute diverticulitis is treated by bed rest application of heat to the abdomen and sulfonamides penicillin or streptomycin or a combination of these Antispasmodics such as atropine (0 6 mg four times daily) are administered *to the point of* tolerance A soft bland diet is recommended

The complications of diverticulitis (perforation abscess or chronic obstruction) are treated with sulfonamides and antibiotics and frequently require a temporary diverting colostomy followed later by resection of the involved colon and closure Primary segmental resection with an end to end anastomosis in one stage is reserved for patients with repeated attacks of diverticulitis who are operated on during the interval phase after the inflammatory reaction has subsided

CANCER OF THE COLON AND RECTUM

Cancer of the rectum and colon is responsible for approximately 16 per cent of all cancer deaths the region ranking second only to the stomach as the most common site of malignancy of the digestive tract It causes about 27 000 deaths in the United States yearly and occurs more commonly in men than in women—usually in the fifth sixth and sev

the reach of the proctosigmoidoscope Barium enema and air contrast studies are diagnostic in the vast majority of cases (over 90 per cent) although less accurate in the rectum and rectosigmoid areas than elsewhere Criteria for malignancy are (1) a persistent filling defect whose outline is irregular and stiff (2) strictures or persistent annular narrowing of the bowel (dilatation or distention of the colon above a tumor is common) (3) persistent obstruction to the flow of barium and (4) infiltration and ulceration with loss of normal mucosal pattern (Fig 185) The oral barium meal is strongly contraindicated in obstructing growths since it may produce acute intestinal obstruction

Differential Diagnosis The differential diagnosis of malignant tumors of the colon on the left side include (1) irritable colon (2) diverticulitis (3) chronic ulcerative colitis (4) fecal impaction (5) hemorrhoids (6) benign tumors and (7) lymphogranuloma venereum Lesions in the right half must be differentiated from (1) regional enteritis (2) appendical abscess (3) renal neoplasm (4) gastric cancer (5) peptic ulcer (6) gallbladder disease (7) blood dyscrasias with anemia (8) tuberculosis (9) amebic abscess and (10) carcinoid tumors

Complications The complications of carcinoma of the colon are often responsible for the presenting symptoms

Partial *obstruction* occurs in approximately 40 per cent of all colon cancers and in 75 to 80 per cent of left colon tumors particularly in the rectosigmoid The obstruction usually develops slowly but may be precipitated suddenly by *impaction* with feces or barium local edema *volvulus* or *intussusception* of the tumor

Ulceration particularly of the nodular and colloid type of adenocarcinoma produces gross or microscopic bleeding *Secondary infection* and *necrosis* may lead to *perforation peritonitis abscess* and *fistula* formation Pressure of the tumor upon the ureter results in *hydronephrosis*

Treatment The only effective treatment is surgical removal of the tumor by resection Combined abdominoperineal resection of the rectum with a permanent abdominal colostomy offers the best opportunity for cure of cancer of the rectum and may be performed as a one stage procedure In selected cases in which the tumor is located above the peritoneal reflection (10 to 15 cm from the anal canal) segmental resection may be performed without a colostomy and with preservation of the anal sphincter Palliative resection is indicated whenever possible despite distant metastases The resectability rate for cancer of the colon and rectum approximates 60 to 70 per cent and is higher in the right half of the colon than the left The surgical mortality ranges between 3 and 10 per cent

Prognosis Five year cures approximate 45 per cent for resectable cancers of the colon and rectum Only 26 per cent of all patients entering the hospital with cancer of the colon and rectum survive 5 years however Lymphatic metastases can be demonstrated in 53 per cent of all patients operated upon for colonic or rectal cancer Duke s classification of tumors establishes the prognosis upon the extent of tumor growth and the presence and extent of lymphatic metastases The 5 year survival rate (60 per cent) is considerably higher in selected patients in whom there is no lymphatic spread Carcinomas of the colon may remain localized for long periods before metastasizing The colloid carcinoma malignant melanomas epithelioma and lymphomatous sarcoma offer the poorest outlook The prognosis is less favorable in the younger age group and is better in women than in men

POLYPS OF THE RECTUM AND COLON

The adenomatous polyp is the most common benign tumor of the colon and rectum occurring in 7 to 9 per cent of the adult population—more often in men than in women and more frequently in the older age groups although it is seen at all ages The polyps may appear singly or as multiple sessile or pedunculated polypoid tumors

Benign mucosal *adenomatous polyps* are particularly significant since they often undergo malignant change and are found in 25 per cent of all resected cancers of the rectum and colon The distribution of adenomatous polyps in the rectum and colon closely parallels that of carcinoma A high percentage of malignant lesions of the colon and rectum originate in preexisting benign mucosal polyps and all stages between benign polyps and carcinoma can be demonstrated histologically Approximately 75 per cent of adenomatous polyps are in the rectum or sigmoid and the remainder are distributed in the middle and upper sigmoid (15 to 20 per cent) and ascending transverse and descending colon Multiple polyps are common (Fig 186)

The *papillary adenomas* constitute 15 per cent of all rectal polyps They are soft velvety villous projections with fine papillary folds involving a wide area of bowel and extending by epithelial proliferation They differ from adenomatous polyps in that they are tumors of the mucosal epithelium rather than of the mucosal glands and they invariably recur after fulguration These tumors are potentially highly malignant

Diffuse familial polyposis (polyposis intestinalis) involving the entire colon and rectum is found in



FIG 185 Annular carcinoma of the sigmoid at the junction of the sigmoid and descending colon Note the greatly narrowed lumen and the ragged napkin ring tumor encircling the colon Histologic examination revealed a poorly differentiated adenocarcinoma of the colon which completely infiltrated the wall

incomplete evacuation Gross bleeding is more common earlier in rectal cancer A decrease in the caliber of the stool occurs when the anus is involved or when anal spasm results from a lesion higher up

Carcinoma of the Right Half of the Colon Carcinoma of the right colon often produces nonspecific abdominal symptoms which are ill defined evanescent and often indistinguishable from those of the irritable bowel syndrome Constipation or diarrhea may occur but are less common than with carcinoma of the left colon Tumors in the hepatic flexure or transverse colon may produce cramping or colicky pain in the right lower quadrant simulating appendicitis Melena is rare *Anemia without* visible blood loss is common occurring in 25 to 50 per cent of patients and may be the cause of the presenting symptoms of weakness and fatigue A mass may be discovered in the right lower quadrant in 5 to 10 per cent of patients

Sarcomas and carcinomas are similar in their clinical pattern although sarcomas occur in younger persons present a more rapid clinical course with more pain and less tendency to hemorrhage and obstruction

Physical Examination There are usually no physical findings early in the disease Pallor resulting from anemia may be evident with lesions of the cecum and ascending colon before weight loss cachexia and other late signs of malignancy are apparent A tumor mass which is hard nodular nontender and fixed may be palpable abdominally

As already stated approximately 70 per cent of all rectal tumors are within reach of the index finger on rectal examination An extrarectal tumor mass in the sigmoid (or cecum) may be felt through the anterior wall of the rectum above the prostate in males (Blumer s shelf)

Audible or visible peristalsis abdominal distention and tympanites characterize obstructing lesions in the left half of the colon Hepatomegaly with or without ascites and lymphadenopathy signify metastases

*Laboratory Findings Anemia is present in two-*thirds of the patients with cancer of the cecum and ascending colon and is found in only one *third or less of patients with cancer of the left half* of the colon Macrocytic anemia observed with right side tumors in the absence of blood loss is unexplained and has been attributed both to an absorptive defect and to marrow suppression by the tumor itself Leukocytosis is absent unless secondary infection intervenes Occult blood is present in the stools of the majority of patients although negative stools do not exclude the diagnosis

Diagnosis The diagnosis of carcinoma of the colon is suggested by one or more of the following (1) vague dyspeptic symptoms weight loss and weakness (2) anemia without visible blood loss (3) a palpable mass by rectal or abdominal examination (4) alteration of bowel habit with alternating periods of diarrhea and constipation (5) *changes in the caliber of the stool (6) acute* subacute or chronic colonic obstruction (7) passage of blood bright or dark red with the stool Proctosigmoidoscopy barium enema and biopsy establish the diagnosis

Proctosigmoidoscopic Examination Approximately 70 per cent of all cancers of the colon and rectum can be visualized through the sigmoidoscope The direct visualization of a tumor particularly in the rectosigmoid where roentgen *diagnosis may be difficult is indispensable* The appearance of a polypoid nodular or ulcerated tumor is usually unmistakable Biopsy is helpful in establishing the diagnosis

Roentgen Examination Roentgen examination is indispensable for the diagnosis of tumors beyond

be considered premalignant lesions and removed whenever possible Adenomatous polyps of the rectum and sigmoid within the reach of the sigmoidoscope may be removed by excision and fulguration Polyps located beyond the reach of the sigmoidoscope are removed preferably by segmental resection of the involved colon particularly if the polyps are multiple Solitary polyps may be excised by polypectomy including a narrow elliptical portion of the wall of the bowel Adenomatous polyps demonstrating malignant change may require radical resection Papillary adenomas demand radical resection with or without preservation of the sphincter if the diagnosis is established by biopsy and inspection Repeated follow up sigmoidoscope and roentgen examinations at regular intervals are essential for all patients with rectal and colonic polyps because of the high incidence of recurrence and the later development of cancer Polyposis of the congenital type is treated by resection of the entire colon and rectum because of its highly malignant nature

OBSTRUCTION OF THE COLON AND RECTUM

Obstruction of the large bowel deserves special consideration because of inherent differences from small intestinal obstruction in respect to etiology symptomatology and treatment

Etiology *Chronic Obstruction* Primary *carcinoma* of the sigmoid flexure and rectum is the most common cause of chronic obstruction of the large bowel Next in frequency are *diverticulitis* and *inflammatory strictures* (ulcerative colitis lymphogranuloma venereum bacillary dysentery typhoid) Chronic obstruction may result from (1) fecal impaction (2) megacolon (3) endometriosis (4) large polyps (5) pelvic infections and tumors (6) traumatic strictures (mechanical or operative) (7) irradiation reaction following treatment of cancer of the cervix and (8) congenital anomalies (imperforate anus rectal malformations)

Acute Obstruction In contrast to the situation in the small intestine where adhesions and hernia are most often responsible for acute obstruction (77 per cent) primary *carcinoma* is the most common cause of *acute* obstruction of the large bowel Next in order of frequency are *volvulus diverticulitis* and *intussusception*

Volvulus signifies torsion or twisting of a segment of bowel on its mesenteric axis usually in a clockwise direction Defective fixation of the mesentery a long flexure or an unusually long mesenteric attachment may predispose to its occurrence The ileocecal area (in children) and the sigmoid (in adults) are the most frequent sites Circulatory disturbances occur early and result in venous engorgement edema infarction gangrene and perforation

Intussusception is the invagination or telescoping of one portion of the intestine (intussusceptum) into an adjacent distal segment and occurs most commonly in children usually males Contributing factors in adults are pedunculated tumors cancer Meckel s diverticulum and foreign bodies Intussusception is seen most frequently at the ileocecal junction Edema hemorrhage and induration of the intussusceptum may be followed by ulceration gangrene and perforation of the bowel

Reflex ileus (paralytic ileus) and *metabolic ileus* are discussed elsewhere (Chap 5)

Vascular Occlusion This form of obstruction is caused by interruption of the normal blood supply to the bowel as a result of embolism or thrombosis of the mesenteric vessels

Physiology and Pathology The pathologic physiology of acute *small intestinal obstruction* differs from that of acute colonic obstruction In the small intestine there is a progressively increasing collection of fluid and gas above the obstruction producing progressive distention resulting in edema ulceration inflammatory changes and ischemia of the bowel wall above the site of obstruction Large amounts of fluid electrolytes and plasma escape directly into the lumen of the intestinal tract causing dehydration hemoconcentration hypochloremia alkalosis or acidosis hypoproteinemia hypopotassemia and azotemia

Acute *obstruction of the colon* rarely produces this picture of severe chemical imbalance The obstruction in the large bowel may be of the closed loop type because of a competent ileocecal valve which permits gas and fluid to enter the colon from the ileum but prevents their return into the small intestine Consequently there is little or no distention of the small bowel The distention of the large intestine may be extreme because of the accumulation of a large amount of fluid and gas presenting an acute surgical emergency requiring colostomy or cecostomy Extensive inflammation edema ulceration focal necrosis perforation and peritonitis result if decompression is not performed promptly

Symptoms Colonic obstructions except for volvulus and intussusception are often insidious in onset and may present a history of previous mild attacks suggesting incomplete obstruction This is particularly true of carcinoma and diverticulitis An abrupt onset similar to that seen in small intestinal obstruction usually occurs with volvulus and intussusception The characteristic symptoms of chronic large bowel obstruction are (1) insidious progressive con

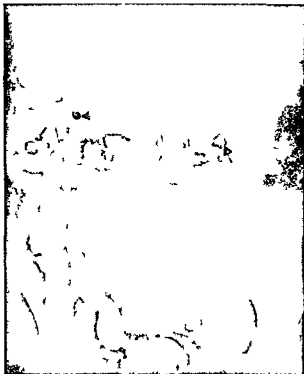


FIG 186 Polyps in the ascending and transverse colon in a 44 year old woman complaining of rectal bleeding

childhood adolescence or early adult life and is classified as the congenital type of polyposis inherited as a simple dominant mendelian trait (Fig 187) Malignant degeneration occurs invariably in this disease *Pseudopolyps* associated with inflammatory diseases such as ulcerative colitis are not true adenomas although they may predispose to cancer

Other less common benign tumors include fibromas *lipomas myomas angiomas adenomyomas* and enterogenous and gas cysts

Diagnosis More than 75 per cent of all benign polyps may be visualized and biopsied through the sigmoidoscope Radiographic studies by air contrast techniques are often necessary to demonstrate polyps and other tumors beyond the reach of the sigmoidoscope

Symptoms Benign tumors and adenomatous polyps may produce no symptoms Bleeding is the most common presenting complaint Less than one third of the patients experience rectal bleeding cramplike abdominal pain or diarrhea although persistent occult blood in the stools may be present more frequently Solitary pedunculated tumors may cause intermittent colicky pain colonic obstruction or intussusception Lipomas are prone to intussusception hemangiomas to bleeding

Treatment Surgical resection of benign tumors *such as fibromas and lipomas* is the procedure of choice All polyps of the rectum and colon should

FIG 187 (*Upper*) Diffuse polyposis of the familial type involving the entire colon and rectum of a 29 year-old male complaining of diarrhea tinged with bright red blood weakness and fatigue (*Lower*) Resected specimen of colon demonstrating extensive polyposis These were benign adenomatous polyps which extended from the ileocecal valve to within 1 cm of the anal orifice

patients with intestinal obstruction are the correction of fluid and electrolyte disturbances removal of the obstructive agent and restoration of normal bowel function This may be accomplished by (1) administration of fluids electrolytes blood and plasma, (2) decompression of the distended intestine by intubation, enterostomy or colostomy and (3) surgical correction and removal of the obstructing mechanism

Fluid electrolyte and vitamin replacement therapy and maintenance of caloric and nitrogen balance must be individualized for each patient, depending upon the level, type and duration of the obstruction and upon his clinical state The principles of such therapy in this condition are discussed in Chaps 48 and 49 Shocklike states accompanying vascular obstruction such as mesenteric thrombosis or embolism volvulus, intussusception and strangulation often require whole blood or plasma transfusions

Obstruction of the colon constitutes an acute surgical emergency in (1) acute closed loop obstruction (2) strangulating obstruction regardless of cause (3) intussusception and (4) volvulus Acute closed loop obstruction requires decompression cecostomy or colostomy Strangulation necessitates laparotomy with removal of the gangrenous segments of bowel The management of intussusception may vary In selected cases reduction by barium enema is successful, but it should be performed under surgical supervision with adequate preparation for prompt operative intervention Volvulus of the sigmoid uncomplicated by strangulation may be treated by sigmoidoscopic decompression with a soft rubber tube Carcinoma of the colon associated with complete obstruction requires preliminary decompression by cecostomy or colostomy Usually the obstruction is incomplete however and adequate decompression may be attained by the use of sulfonamides or antibiotics cleansing enemas, and a bland diet Obstructing cancer of the colon can be decompressed by intubation if the ileocecal valve is incompetent Decompression of the intestinal tract by intubation is often effective in the treatment of paralytic ileus

Drugs which stimulate peristaltic activity as well as the use of enemas have only a transient effect on paralytic ileus and are contraindicated in acute mechanical obstruction of the small intestine or colon

Antibiotics such as penicillin and streptomycin and the sulfonamides may be of value in the treatment of obstruction and are indicated particularly when surgical intervention is anticipated

The choice of the surgical procedure depends upon the cause of the obstruction, viability of the bowel and the clinical state of the patient

CONGENITAL ANOMALIES

Megacolon

Two types of congenital megacolon are encountered Hirschsprung's disease and idiopathic megacolon

Primary megacolon or Hirschsprung's disease is a congenital dilatation elongation and hyper trophy of the sigmoid colon involving at times the entire colon and accompanied by the retention of enormous amounts of feces (Fig 188)

Hirschsprung's disease is characterized by a functionally abnormal narrowed segment of bowel involving the rectosigmoid and rectum with a dilated and hypertrophied colon above (Fig 188) The cause of the narrowed segment has been attributed to the absence of ganglion cells in Auerbach's plexus resulting in an "obstructive" segment on a neurogenic basis

The symptoms appear at birth or during infancy and are more common in males Constipation is often so severe that weeks or months may elapse without a spontaneous evacuation Abdominal distension with gas may be pronounced and intermittent acute attacks of obstruction and vomiting are common Hyperactive peristalsis manifests itself by loud resounding borborygmi Rectal examination reveals an empty rectum and an impacted sigmoid colon Demonstration by roentgenogram of a narrowed rectum and rectosigmoid with marked dilatation of the sigmoid colon establishes the diagnosis (Fig 188)

Medical management is ineffectual in Hirschsprung's disease The most satisfactory surgical procedure consists of an abdominal resection of the narrowed aganglionic distal segment (rectum and rectosigmoid) with a "pull through" anastomosis preserving the anal sphincter

Idiopathic megacolon differs significantly from Hirschsprung's disease (1) It may not become evident symptomatically until 2 to 3 years or more after birth (2) Abdominal distention occurs less commonly constipation is less pronounced and vomiting is infrequent (3) Impactions are found within the rectum (4) A narrowed segment cannot be demonstrated roentgenologically and the entire rectum and rectosigmoid appear dilated

Treatment consists of a bland low residue diet, enemas mineral oil or other laxatives and cholinergic drugs

Other Anomalies of the Anus Rectum and Colon

Other congenital anomalies include redundant colon anomalies of rotation descent and fixation duplication and triplication of the colon atresia of the anal canal rectum or sigmoid imperforate anus and congenital strictures of the rectum

stipation (2) distention without vomiting and (3) colicky recurrent abdominal pain

Constipation is common in all forms of obstruction after the intestine distal to the occlusion has been emptied Obstipation and the inability to expel flatus often follow Paradoxical diarrhea may occur if liquid feces pass around an impaction or tumor in a dilated rectum

In contrast to the frequent and copious vomiting associated with high obstruction of the small intestine vomiting is frequently absent in colonic obstruction in spite of severe distention Marked distention without vomiting is particularly characteristic of closed loop obstruction described previously

In colonic obstruction intermittent colicky abdominal pain may be absent or is frequently atypical and should not be regarded as a presenting or essential sign This is in sharp contrast to small bowel obstruction in which severe intermittent colicky midabdominal pain characteristically occurs in paroxysms increases rapidly to a peak in crescendo fashion and remains sustained at its maximum intensity usually for 1 to 3 min before ceasing abruptly There is usually no pain between paroxysms except with strangulation when the pain becomes constant

With increasing distention the contractability of the colon is diminished and the colic decreases in severity Pain is frequently absent in functional ileus and tends to be rhythmic in intussusception

Blood in the stools in acute colonic obstruction suggests cancer diverticulitis, or strangulation Vascular occlusion is accompanied by acute abdominal pain tenderness and rigidity shock rapid pulse and respiration vomiting or diarrhea The passage of blood and mucus by rectum in children with periodic attacks of abdominal pain vomiting and a palpable tumor indicates intussusception Extreme fulminant distention developing in a very short time is characteristic of volvulus of the right or left colon

Physical Findings During the early postobstructive period the patient usually presents no significant change in appearance As the disease progresses a shocklike picture may develop if strangulation and impairment of blood supply intervene Dehydration and electrolyte imbalance are less likely to occur in colonic obstruction in contrast to small intestine obstruction

Abdominal examination reveals distention tympanites abnormal peristaltic activity and variable degrees of abdominal tenderness depending upon the cause of the obstruction In simple obstruction the abdominal wall may remain soft and nontender although some tightening of the abdominal muscles may be discernible during paroxysms of colic

In carcinoma a palpable abdominal tumor is an important diagnostic clue A sausage-shaped mass of an advancing intussusception is a significant diagnostic sign particularly in children

Interference with the blood supply accompanies volvulus or intussusception and may be caused by overdistention of the bowel from any cause Perforation and leakage are manifested by abdominal tenderness increased pulse rate rigidity or a mass Abdominal tenderness may be present directly over a distended twisted loop of bowel in volvulus or over an obstructing carcinoma or area of diverticulitis

Auscultatory findings are often significant Characteristically borborygmi may be heard at the height of the attacks of pain Its concomitant occurrence with each paroxysm indicates intestinal colic The loud gurgling bubbling noises may assume a metallic tinkling character as the obstruction progresses In adynamic ileus and the late stages of obstruction the abdomen becomes silent

The presence of a mass or stricture on rectal examination may reveal the source of the obstruction

Diagnosis. The laboratory studies in large-bowel obstruction may reveal anemia or hypoproteinemia on the basis of blood loss or malnutrition in contrast to the dehydration and hemoconcentration commonly seen in small intestine obstruction In the early phase of colonic obstruction the laboratory studies are essentially normal except perhaps for persistent occult blood in the stools

Roentgen examination is one of the most valuable procedures in diagnosis "Scout" films of the abdomen taken with the patient in the erect and supine positions will aid in localizing the site of obstruction by the distribution of gas and fluid levels in the small intestine or colon Roentgenograms taken with the patient in an upright position may reveal numerous fluid levels in dilated loops of bowel one above the other in a step-ladder pattern indicating small intestinal obstruction Distention limited entirely to the colon is evidence of complete competency of the ileocecal valve and often presents a classic roentgen picture The characteristic roentgen picture of volvulus is that of extreme distention restricted to a closed loop of colon In sigmoid volvulus the distended colon appears on the right side and in cecal volvulus on the left

A barium enema may be helpful in determining the site of occlusion Barium by mouth is contraindicated in cases of suspected intestinal obstruction Proctosigmoidoscopy with biopsy may often establish the diagnosis particularly in chronic obstruction caused by carcinoma

Treatment The objectives in management of

or cotton after defecation witch hazel packs bland *ointments or calamine* lotion may be helpful Subcutaneous injection of the area with alcohol x ray therapy and hydrocortisone ointment have also been recommended

STRICTURES AND FISTULAS

The most common causes of strictures are cancer ulcerative colitis diverticulitis lymphogranuloma venereum operative procedures and radiation therapy Other inflammatory and granulomatous processes which may result in stricture formation are typhoid fever bacillary dysentery regional enteritis tuberculosis and syphilis

Fistulas may arise as a complication of surgery or a number of diseases including ulcerative colitis diverticulitis regional enteritis tuberculosis lymphogranuloma venereum and actinomycosis

LYMPHOGRANULOMA VENEREUM

This subject is discussed in Chap 188

COMPLICATIONS OF ANTIBIOTIC THERAPY

The administration of broad spectrum antibiotics (Aureomycin Terramycin, and chloramphenicol) may produce gastrointestinal disorders such as stomatitis monilial infections blacktongue proctitis epigastric or abdominal pain nausea vomiting diarrhea rectal bleeding intestinal deficiency patterns and pruritus ani presumably as a result of drug toxicity or alteration of the bacterial flora These complications are usually self limited and subside soon after the antibiotic is discontinued

Pseudomembranous Enterocolitis

This fulminant frequently fatal disease may be seen as a complication of antibiotic therapy alone or may occur after a wide variety of surgical procedures unrelated to the preoperative administration of broad spectrum antibiotics The syndrome appears to be related to an altered intestinal bacterial flora and an overgrowth of *Micrococcus pyogenes* organisms (*Staphylococcus aureus*) which are often found in the stools and intestinal lesions in pure culture

Symptoms The onset is usually abrupt and the clinical course rapid and progressive often leading to death in a few hours or days The disease is characterized by diarrhea fever cramping abdominal pain and distention nausea vomiting and profound circulatory collapse Severe diarrhea with passage of membranous shreds blood and pus is usually but not invariably observed Shock mental confusion or delirium dehydration oliguria and fluid and electrolyte imbalance are common

Pathology The mucosal surface of the bowel is covered by a yellow green or grayish brown friable pseudomembrane which may be observed anywhere from the esophagus to the rectum The small intestine and colon are most frequently involved The mucosa becomes necrotic peels off and forms a diphtheritic membrane containing cellular debris and bacteria Characteristically there is extensive denudation of the mucosa of the bowel and the colon contains tremendous quantities of fluid and gas Peritonitis is common

Etiology The cause of the disease is unknown The two dominant factors appear to be infection and tissue necrosis The choleralike state and the diffuse necrosis of the gastrointestinal mucosa have been attributed to the growth of resistant strains of *Micrococcus pyogenes* which elaborate exotoxins and endotoxins These organisms grow rampant on necrotic tissue particularly when other bacteria have been eliminated by antibiotic therapy Shock arteriolar vasospasm and intravascular clotting in the mucosal capillaries of the intestine are contributing factors in the tissue necrosis The syndrome has been observed following the use of any broad spectrum antibiotic but it existed postoperatively before the antibiotic era

Diagnosis The disease should be suspected in any instance of severe diarrhea particularly if fever toxicity and signs of circulatory collapse develop postoperatively or during antibiotic therapy Sigmoidoscopy may reveal an edematous friable necrotic mucosa resembling that of nonspecific ulcerative colitis *M pyogenes* organisms are usually demonstrable in stool cultures The syndrome may simulate peritonitis intestinal obstruction ulcerative colitis amebic or bacillary dysentery coronary thrombosis or pulmonary embolism

Treatment Treatment must be prompt and energetic Erythromycin (500 mg or more four times daily depending upon bacterial sensitivity) should be administered promptly and all other antibiotics discontinued In some instances the newer antibiotic Novobiocin (500 mg every 8 hr) may be more effective Vigorous replacement of fluids and electrolytes is essential Blood transfusions may be helpful in combating shock The administration of 20 mg corticotropin intramuscularly three times daily for 4 to 10 days has been recommended

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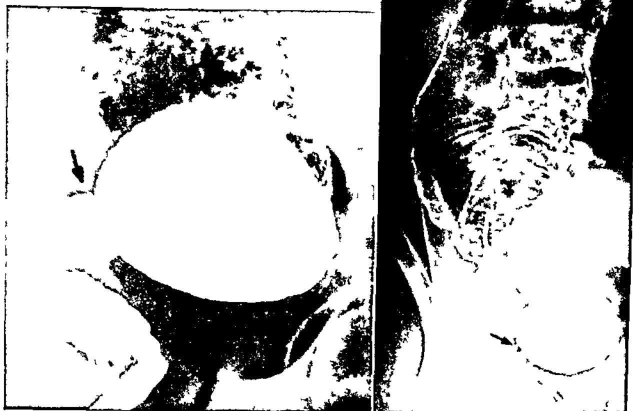


FIG 188 *Congenital megacolon (Hirschsprung's disease)* Note the contraction ring at the junction of the rectum and sigmoid with tremendous dilatation of the sigmoid colon above

HEMORRHOIDS

Hemorrhoids are superficial varices which appear at the anorectal junction Internal hemorrhoids arise above the anorectal junction and are covered with mucous membrane External hemorrhoids arise below the pectinate line and are covered with skin The most common contributing factors are constipation straining at stool chronic diarrhea heavy lifting or overexertion pregnancy tumors portal obstruction or any cause of increased intraabdominal pressure The sudden onset of pain and the presence of a firm tender localized swelling at the anal region indicate thrombosis Hemorrhoidal bleeding of bright red blood usually streaking the outside of the stool may produce chronic blood loss and anemia The diagnosis is made by history digital examination and direct examination through the anoscope

Treatment consists of correction of the constipation and diarrhea avoidance of straining at stool the use of mineral oil or rectal suppositories application of wet packs after defecation bland ointments and sitz baths In selected cases hemorrhoids which bleed and do not prolapse may be treated by injections of sclerosing solutions A thrombus may be removed by simple incision Excision of internal and external hemorrhoids is usually performed to alleviate pain and bleeding or because of prolapse perianal seepage infection and pruritus Surgery should never be performed without a previous proctosigmoidoscopy to exclude rectal cancer polyps or ulcerative colitis Hemorrhoidectomy is contraindicated in the presence of acute inflammation and ulcerative colitis

PRURITUS ANI

Intractable itching of the perianal area usually worse at night has been attributed to emotional difficulties hemorrhoids cryptitis proctitis fungous infections worms chemical irritants endocrine disorders allergic factors and antibiotics The exact mechanism is unknown There is no specific treatment Careful cleansing of the area with soft tissue

tension gastric varices and congestive splenomegaly Thrombosis or erosion of the splenic vein is an occasional complication of pancreatitis

Pancreatic Function Tests Pancreatic function tests depend on demonstrating either excessive amounts of pancreatic secretory products in the blood or insufficient amounts in the digestive tract Normal serum amylase concentration is less than 150 Somogyi units per 100 ml and lipase less than 1.5 Cherry Crandall units per 1 0 ml Trypsin inhibitors interfere with the direct determination of this enzyme in the blood but indirect evidence of proteolytic action may be detectable in that prothrombin and antitrypsin titers are depressed and fibrinolytic and antithrombic activities increased if pancreatic proteases accumulate in the blood Various "provocative" tests have also been advocated blood levels of amylase are measured before and after giving (1) morphine to increase sphincter of Oddi resistance and (2) secretin or a cholinergic agent to stimulate pancreatic secretion Because varied combinations of effects are possible these procedures are not reliable

Urinary concentrations of diastase reflect serum amylase changes but are more erratic The role of urinary lipase determinations is unsettled

Direct measurement of pancreatic secretion is accomplished by quantitative collection of duodenal contents after stimulation with secretin to increase volume and bicarbonate output or after cholinergic stimulation of enzyme output Following secretin stimulation the normal pancreas puts out a minimum of 2 ml per kg of juice per 80 min and a concentration of 90 mEq of $NaHCO_3$ per liter Rough tests for the presence of pancreatic ferments in the feces (i e gelatin film test) are not useful in adult patients

Indirect evidence of pancreatic exocrine function is obtained by various tests of absorption In general all tests in which a substance is administered by mouth and blood levels are subsequently measured are unsatisfactory because blood levels are affected by so many functions Examination of the feces for excessive loss of fat or protein is more reliable but abnormalities indicate impaired absorption not necessarily impaired pancreatic digestion Long term balance studies are probably most accurate satisfactory results can be obtained by the simpler method of measuring the fecal loss of I^{131} labeled fat or protein and microscopic examination of the stool for meat fibers and fat droplets (proper preparation of the specimen with 30 per cent acetic acid heat and sudanophilic stain is essential) is a rough test suitable for preliminary study and detection of advanced pancreatic insufficiency

Although abnormal glucose metabolism is a frequent manifestation of pancreatic disease evidence of such an abnormality is obviously not specific for infections or tumors of the pancreas

ACUTE PANCREATITIS

Acute pancreatitis is divided into the edematous hemorrhagic and necrotic varieties according to the pathologic change that predominates Although the clinical and pathologic features of the three types vary their pathogenesis is presumably the same and such differences as exist are attributable to the degree of pancreatic damage

Etiology Acute pancreatitis tends to occur in patients with alcoholism gallstones and peptic ulcer occasionally it appears as a complication of pregnancy essential hyperlipemia and diffuse vascular disease such as periarteritis nodosa A not infrequent cause is trauma either indirect as from a heavy abdominal blow or direct as from surgery in the upper abdomen Pancreatitis also appears in normal persons following a heavy meal and sometimes has no recognizable antecedent

The pathogenesis of pancreatitis presumably depends on intrapancreatic activation of proteolytic enzymes with consequent digestion of pancreatic tissue and blood vessels Such pancreatic autodigestion apparently may develop under two general conditions (1) when pancreatic secretion is obstructed either by a solitary lesion of a major duct or by diffuse blockage of many tiny ductules or (2) when acinar tissue is exposed to direct injury by toxins ischemia inflammation or trauma. Experimentally for example pancreatitis can be initiated by the combined procedure of obstructing the pancreatic ducts and injecting agents such as bile or bacteria to activate proteolysis This fact lends credence to the hypothesis that pancreatitis may develop if a stone in the ampulla of Vater or a spasm of the sphincter of Oddi impedes pancreatic secretion with reflux of bile into the pancreatic ducts Arguments against this theory are as follows reflux of bile into the pancreatic ducts may occur without untoward effects the secretory pressure of the pancreas equals or exceeds that of the biliary system and a common channel of pancreatic and common ducts long enough to permit reflux probably exists in less than 50 per cent of people

Direct injury to acinar tissue would appear to be responsible for the pancreatitis that follows pancreatic trauma or a penetrating peptic ulcer In animals the tissue damage and ischemia produced by a local Shwartzman reaction or by injection of staphylococcal toxin into the pancreatic ducts induces a fulminating pancreatitis The nature of alcoholic pancreatitis is obscure alcohol does not appear to have a direct effect on pancreatic function It has however been suggested that chronic pancreatitis in alcoholics may be a deficiency dis

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249 DISEASES OF THE PANCREAS

Franz J Ingelfinger

Symptomatology The outstanding symptom of pancreatic disease is pain In addition pancreatic disorders may produce symptoms by altering the structure and function of any of the following systems (1) the pancreatic acini and ducts (2) the islands of Langerhans (3) the biliary passages (4) the gastrointestinal tract and (5) the portal circulation

Pain The pain of pancreatic disease roughly corresponds in location to the position of the lesion but its character is capricious and its borders are indeterminate Presumably made up of both true visceral and referred somatic components pancreatic pain is felt between the xiphoid and umbilicus in front and between the tenth thoracic and second lumbar vertebrae in back Frequently it bores through the body from front to back or vice versa but superficial radiation along the costal margin is unusual Because of the central position of the pancreas and its bilateral sensory innervation pain from a lesion confined to the head or tail tends to be felt centrally but with increased emphasis to right or left depending on the position of the lesion

Abnormalities of External Secretion The pancreatic juice amounting approximately to 1 500 ml per day contains water bicarbonate (60 to 120 mEq per liter) sodium (140 mEq per liter) potassium (4 mEq per liter) smaller quantities of other ions and numerous digestive ferments classified under the broad headings of trypsin amylase (diastase is used as an equivalent term) and lipase Loss of this entire secretion through an external pancreatic fistula leads to dehydration and electrolyte depletion In addition deviation of the pancreatic enzymes from the gut causes a fecal loss of about half the fat and 30 per cent of the protein ingested Carbohydrate is also digested poorly but hydrolysis by intestinal bacteria prevents its loss in the feces Similar absorptive defects follow total pancreatectomy complete obstruction of the ducts or extensive destruction of the gland by disease On the other hand subtotal resection of the pancreas or incomplete involvement by disease usually does not bring about obvious steatorrhea (fecal fat loss) or creatorrhea (fecal protein loss) since the reserve capacity of the surviving pancreatic acini is tremendous In dogs digestion may be unimpaired after resection of four fifths of the pancreas

Abnormalities of Internal Secretion The islands of Langerhans often remain relatively unaffected by inflammatory or neoplastic lesions of acinar tissue Consequently diabetes is often mild or even absent in the face of extensive pancreatic disease Total pancreatectomy in man is compatible with life provided that insulin requirements (about 50 units per day) are met and digestion is aided by oral administration of pancreatic material The suggestion that the islet cells elaborate a lipotropic hormone (lipocaic) has not been accepted Inadequate digestion and absorption of nitrogenous substances probably account for the fatty liver that attends total pancreatectomy in dogs

Disorders of the Biliary Passages Lesions in the head of the pancreas may obstruct the common bile duct producing jaundice Without a complicating infection such purely mechanical obstruction of 3 weeks duration or less rarely affects the liver seriously especially if a normal gallbladder is present (see Chap 251) It is possible but not established that reflux of normal or infected pancreatic juice into the biliary system may initiate disease in this organ

Gastrointestinal Disorders Nausea vomiting belching bloating distention or diarrhea are caused partly by the malabsorption of pancreatic insufficiency and partly by direct irritation or reflex stimulation of gastrointestinal motor function Digestive disorders also arise if the alimentary organs are displaced or compressed by pancreatic tumor and direct invasion of the stomach duodenum or transverse colon by cancer of the pancreas may lead to mechanical obstruction or bleeding

Disorders of the Portal Venous System Because of the intimate anatomic relationship of the splenic and portal veins and the pancreas hematogenous metastases to the liver are an early possibility in pancreatic cancer and neoplastic obstruction of the portal venous system may produce portal hyper

Table 127 DIFFERENTIAL DIAGNOSIS OF ACUTE PANCREATITIS

Disease	History	Physical examination	Laboratory findings
Acute pancreatitis	Sudden onset often with immediate maximal development of pain Past or recent history of gallstones alcoholism peptic ulcer dietary debauch trauma or upper abdominal surgery	Abdominal findings moderate as compared to violence of pain Tenderness extends to left of epigastrium Abdominal distention moderate or absent Peristaltic noises diminished or absent Shock and cyanosis may be striking Patient may be restless	Elevation of amylase in serum and urine Hypocalcemia in severe cases Paracentesis evidence of fat necrosis sometimes sanguineous fluid high amylase levels
Perforated viscus especially peptic ulcer	History of ulcer	Boardlike pain and tenderness in epigastrium Patient fears movement and jarring Shock rare	X ray shows free intraperitoneal air
Mesenteric vascular occlusion	Elderly patient with cardiovascular disease or recent operation Development of pain may be gradual		WBC over 20 000 Paracentesis sanguineous fluid
Acute intestinal obstruction	Intermittent colics with relative comfort between pain Past history of abdominal operation or of inguinal or femoral hernia	Abdominal distention with loud peristalsis Shock rare Patient moves around with colic	X ray of abdomen shows characteristics of mechanical obstruction
Biliary colic	Pain more right-sided more gradual in onset and less prostrating than that of pancreatitis	Tenderness maximal on right side of abdomen	
Coronary occlusion	Pain usually maximal in chest neck or arms	Relatively few abdominal findings Shock and restlessness often present	Electrocardiographic abnormalities
Dissecting aneurysm of aorta		Impaired femoral pulsations Shock and restlessness often present	Hematuria

The points listed are of presumptive importance as guides toward the correct diagnosis but they are not invariable features of the diseases under which they are grouped

retroperitoneal sepsis rupture into a major blood vessel with internal hemorrhage and persistent external pancreatic fistula following drainage procedures The disease may run a slow downhill course characterized by malnutrition ileus and diarrhea

Differential Diagnosis Any severe pain in the middle of the body should suggest pancreatitis A history of previous attacks of pain is common but also characterizes important differential diagnoses Once pancreatitis is suspected its diagnosis can usually be established by measurement of pancreatic enzymes in the blood by exclusion of the conditions most likely to simulate pancreatitis and by the course of the disease In considering the differential diagnoses (Table 127) it is well to remember that coronary occlusion and biliary colic are approximately twenty times as common as acute pancreatitis that perforated ulcer is three times as common that mesenteric vascular occlusion is except in postoperative cases somewhat less common and that a dissecting aneurysm is rarely seen

Elevation of serum amylase levels as occurs in pancreatitis sometimes is seen in mumps in patients given morphine (presumed reason contraction of

ease because chronic pancreatic changes characterize the deficiency disease kwashiorkor and because degenerative lesions can be induced in the pancreas of rats exposed to the methionine antagonist ethionine

Incidence Acute pancreatitis occurs rarely in children but affects adults of any age As might be anticipated from the incidence of the antecedent disorders pancreatitis associated with alcoholism duodenal ulcer or trauma is vastly more common in men than in women but even pancreatitis associated with gallstones is as common in the male as the female in spite of woman s greater tendency to form gallstones

Symptoms Severe upper abdominal pain usually beginning with catastrophic suddenness is the outstanding symptom Its degree varies with the violence of the pancreatic insult but it is rarely less than agonizing In mild (edematous) pancreatitis the patient may content himself with demanding analgesic medication in the hemorrhagic form he is anxious and restless even though motion may aggravate his suffering whereas the pain of necrotic pancreatitis is so severe as to produce shock Though centered initially in the upper midabdomen the violent pain of acute pancreatitis usually diffuses to the back chest and the lower abdomen

Nausea and vomiting abdominal bloating and constipation are frequent complaints Mild jaundice may be detected clinically or biochemically within 1 to 3 days of the onset in 25 per cent of cases In those with alcoholism psychotic episodes may complicate the picture

Physical Examination The patient is obviously distressed and anxious In some patients beads of sweat emphasize an underlying pallor in others subject to severe shock the face is livid and the extremities clammy Fever is usually not present initially and the pulse subject to a variety of defense mechanisms may be slow or fast strong or imperceptible The blood pressure reflects the degree of shock Tenderness voluntary resistance and spasm in the upper abdomen are present to a variable degree but these signs in striking contrast to the intense pain may be remarkably unimpressive Moderate abdominal distension and suppression of peristaltic sounds are frequent findings

Laboratory Data Urinary output is depressed in shock One out of four cases has glycosuria and the incidence of choluria is the same The white count ranges from 8 000 to 20 000 with increased polymorphonuclear cells A striking finding in severe cases is hemoconcentration with hematocrit values at times exceeding 60 per cent Mild hyperglycemia is common not only because of islet cell damage but also because of the patient s reaction to violent stress

The concentration of pancreatic enzymes in the blood provides the most specific laboratory information Within 8 hr of the onset of acute pancreatitis serum amylase values rise in 80 per cent of the cases to values exceeding 250 Somogyi units After 48 hr even in the face of clinical evidence of continuing pancreatitis amylase values tend to return to normal As amylase decreases blood lipase values rise in about half the patients to exceed 2 0 Cherry Crandall units and then subside slowly over a period of days to weeks In severe cases blood calcium levels fall from 3 to 10 days after the onset presumably because calcium soaps form with the fatty acids liberated by lipolytic destruction of abdominal and retroperitoneal fat

X ray Abdominal films may reveal moderately distended gas filled loops of intestine the paralytic ileus particularly affects the jejunal coils near the pancreas

Course Hemorrhagic or necrotic pancreatitis is fatal in over 50 per cent of the cases Almost all cases with edematous pancreatitis recover In the most severe cases death occurs within hours The mildest forms on the contrary subside completely with equal rapidity Most clinically recognized attacks run a course between these extremes Abdominal pain and distention persist or may reappear in bouts of renewed intensity expressing not only further pancreatic injury but also chemical peritonitis which develops as peripancreatic mesenteric and omental tissues are digested Concurrent with fat necrosis a dark bloody and cloudy peritoneal exudate accumulates in amounts ranging from 500 to 2 000 ml The patient at this point is no longer in shock but appears toxic and febrile Hypocalcemic tetany occurs in some cases

Hemorrhagic phenomena manifest at the onset of pancreatitis and reflecting proteolytic injury to clotting mechanisms are seen but rarely Three to six days later however edema and the typical blue green brown discoloration of a hematoma may appear on the abdominal wall either about the umbilicus or in the flanks (Grey Turner sign) The source of the blood is the hemorrhagic pancreas whence blood seeps by retroperitoneal routes to reach the abdominal wall

Late complications of pancreatitis are the formation of abscesses or pseudocysts (see Pseudocysts) an increased susceptibility to further attacks of pancreatitis and chronic pancreatitis The abscesses usually sterile are essentially collections of pancreatic secretions necrotic debris inflammatory cells and tissue fluids Pain fever chills and left sided pleural effusions are often evident The process may subside spontaneously or may drain by rupturing into the alimentary tract but surgical drainage is usually required Serious and life threatening complications are secondary bacterial infections at times by gas forming anaerobes perforation with

are readily palpable Their cystic nature however is difficult to ascertain for the mass as palpated through muscles tensed by considerable guarding may give the impression of hardness Signs of fluid or atelectasis at the left lung base are common X rays establish the location of the tumor and exclude lesions of the gastrointestinal tract and kidneys Jaundice occurs in 10 per cent of the cases

The principal differential diagnosis is upper abdominal neoplasm particularly of the pancreas If an attack consistent with pancreatitis has occurred within months the history is helpful but in approximately one out of three pseudocysts the initiating pancreatitis is mild atypical and unrecognized In these instances the existence of conditions predisposing to pancreatitis such as gallstones alcoholism duodenal ulcer or trauma provides a basis for suspecting a pseudocyst On the whole the patient with pseudocyst though perhaps febrile and distressed is not so debilitated as one would expect were his huge abdominal mass composed of neoplastic cells

In case of doubt exploratory surgery is always warranted Surgical treatment of a pancreatic pseudocyst consists of external or internal drainage or of removal with or without simultaneous resection of pancreatic tissue



Fig 190 Chronic relapsing pancreatitis In this film of the upper abdomen the entire pancreas is shown outlined by extensive calcific deposits

CHRONIC RELAPSING AND CALCAREOUS PANCREATITIS

Chronic relapsing pancreatitis sometimes is initiated by a clear cut attack of acute pancreatitis at other times it begins insidiously with atypical and relatively mild pains Whatever the onset the pancreas undergoes chronic changes consisting of acinar destruction inflammatory reaction interstitial fibrosis and variable damage to the islet cells In about half the cases calcific deposits form in the tubules the pancreatic substance or both (Fig 190) The name *calcareous* or *calcific* pancreatitis is often applied when the pancreas is irregularly calcified but the clinical characteristics are similar to those of chronic relapsing pancreatitis without calcific deposits The formation of pseudocysts is a common complication

As is true of acute pancreatitis the chronic varieties tend to appear in alcoholic patients those with gallstones or peptic ulcer and in those who have had upper abdominal trauma In the past gallstones have been considered as the principal antecedent but at present particularly in males with calcareous pancreatitis chronic alcoholism is the commonest background condition

Although chronic pancreatitis occasionally runs a painless course the outstanding symptoms are recurrent bouts of pain interspersed by periods either asymptomatic or characterized by persistent distress The episodic pains probably caused by limited but acute pancreatic inflammation resemble the pains of acute edematous pancreatitis in their character location and radiation The nature of the chronic distress is unpredictable partly because the patient with relapsing pancreatitis sometimes in alcoholic and sometimes addicted to narcotics after months of agonizing pain is a poor describer of his pains

The changes of chronic pancreatitis are so diffuse that some degree of pancreatic insufficiency is often manifest Because of impaired lipolytic and proteolytic activity digestion is impaired weight loss is striking and fatty and nitrogenous foods are lost in the stools The patient may consider his bowel movements normal but direct questioning reveals that they are bulky light and greasy in appearance and tend to float all indications of steatorrhea Although the absorption of vitamins D and K is impaired tetany and purpura such as occur in sprue are extremely unusual Frank diabetes occurs in only 10 to 15 per cent of the cases but impaired glucose tolerance is found in 75 per cent A few patients for unknown reasons manifest hyper

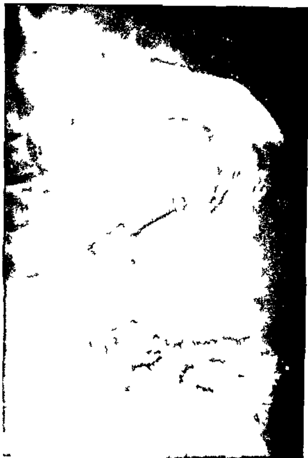


FIG 189 Pancreatic pseudocyst In this lateral view the body of the stomach appears to be pushed forward by a large mass between it and the spine The cause of the pseudocyst is well shown a large penetrating duodenal ulcer

sphincter of Oddi with temporary backing up of pancreatic juice) in perforated ulcer (presumed reason leakage of pancreatic enzymes from duodenal lumen into peritoneal cavity and thence absorption into blood) and in isolated instances of various other conditions particularly mesenteric vascular occlusion

Treatment Direct surgical attack with incision and drainage of the inflamed pancreas has been generally abandoned as ineffective and as incurring the risk of external pancreatic fistula Surgeons who believe that pancreatitis is caused by biliary reflux favor drainage of the common bile duct or the gall bladder in the hope of achieving decompression but the preponderant tendency at present is to treat pancreatitis conservatively

The rationale of therapy is (1) to keep pancreatic secretory activity at a minimum (2) to avoid any increase in ductile obstruction and (3) to prevent potential and treat actual complications Shock and hemoconcentration are treated with parenteral water electrolytes and human albumin Since opiates increase the resistance of the sphincter of Oddi meperidine is recommended on theoretical grounds for relief of pain but proves inadequate in many severe cases In such cases morphine or its derivatives may have to be used Nothing is given by mouth and constant gastric suction is used for several days to reduce intestinal distention and secretin production by the duodenum Fluid salt and small quantities of glucose are given intravenously with temporary disregard of caloric requirements Because secondary infection of necrotic tissue of partially obstructed biliary passages or of atelectatic lung is a dangerous possibility prophylactic daily doses of parenteral penicillin (1 000 000 or more units) and streptomycin (1 Gm) are advisable

Other less routine measures may be used Anticholinergics such as methantheline bromide (Banthine) 25 to 50 mg intravenously or 50 to 100 mg intramuscularly every 6 hr should inhibit the vagal phase of pancreatic secretion but these agents are usually effective only in the milder cases and in them parenteral anticholinergics are indicated Although experimental evidence suggests that inhibition of carbonic anhydrase with acetazoleamide (Diamox) decreases secretin stimulated pancreatic secretion the efficacy of Diamox in the management of pancreatitis has yet to be evaluated Paravertebral splanchnic or epidural procaine block sometimes relieves pain dramatically and some investigators believe that these procedures not only are symptomatic but also actually help the injured pancreas by augmenting its blood supply Hyperglycemia may require control with insulin Hypocalcemia is treated by injections of calcium gluconate 10 ml of a 10 per cent solution (90 mg of Ca) being given slowly by vein The total amount needed is determined by the patient s clinical response and his serum calcium level

As the patient improves foods may be given slowly beginning with a low fat low caloric intake which is increased according to individual tolerance Residual intraperitoneal abscesses may have to be drained eventually

PSEUDOCYSTS

Sometimes the collections of fluid and cellular debris that may follow pancreatitis produce only moderate inflammatory reaction but persist in chronic form for weeks to months Usually situated in the middle or left upper abdomen these pseudocysts may fluctuate in size or may form tremendous masses which create symptoms by pushing the duodenum to the right the stomach forward (Fig 189) the left diaphragm and lung upward and the transverse colon downward Aching distress rather than acute pain is the usual complaint

Pancreatic pseudocysts are tender and usually

creatic cancer jaundice occurs less frequently than weight loss or pain but diagnostically it is the most important symptom *It points specifically to the biliary passages* and *in lesions near the ampulla* of Vater gives early warning before extensive growth or metastasis has taken place The course and intensity of the jaundice depend on the degree of biliary obstruction (Table 128) In advanced cases *of cancer of the head of the pancreas it assumes* a deep greenish brown hue Itching is an associated symptom in three fourths of the cases

Laterally painless jaundice characterizes cancer in the head of the pancreas in only a few cases *More frequently the patient suffers from vague* abdominal distress and fullness sometimes worse sometimes better after eating The severe pain of cancer in the body or tail may however be diagnostic it bores through to the midback when the patient lies supine and he obtains relief only by standing or by sitting hunched up with arms clasped about the knees

Physical Examination Physical examination may reveal nothing except jaundice and the excoriations produced by scratching *In spite of biliary obstruction hepatic enlargement is not* striking unless the liver is involved by metastases or cholangitis or the gallbladder is not functioning In protecting the liver from back pressure however the gallbladder *is itself enlarged in nearly all malignant* obstructions of the common duct but it can be palpated in only half the cases A definite finding of an enlarged nontender gallbladder in a jaundiced patient may therefore be taken as a reliable sign of malignant choledochal obstruction (Courvoisier's law) No diagnostic inference is warranted if the gallbladder is not palpable

In advanced cases abdominal masses enlarged supraclavicular nodes a liver hardened and enlarged by *metastases or evidences of ascites may* be found Splenomegaly does not occur except in the rare case of occlusion of the splenic vein by cancer arising in the pancreatic body or tail In 20 per cent of the cancers at this site spontaneous venous thrombosis of the extremities particularly the legs take place

Laboratory Data The urine blood and feces of nonicteric patients are often normal Those with icterus *manifest persistent and progressive* bilirubinemia and choluria with all the attributes of a regurgitation jaundice (Chap 18) The stools may be greasy abundant of a pultaceous consistence very deficient in bile and most dreadfully foetid (Richard Bright 1833) In at least half the cases however the clay colored stools are not grossly fatty and are more like putty than butter Since bile salts are necessary for the absorption of vitamin K hypoprothrombinemia develops with prolonged biliary obstruction

Since neoplastic cells are in general nonfunctioning and since the functional capacity of surviving *acinar cells is tremendous serum enzyme values are* normal in three fourths of the cases Except in case of very small and nonobstructing lesions the volume of pancreatic juice in response to secretin stimulation is usually reduced Glucose tolerance tests are abnormal in 40 per cent of the cases *but the patient's age or an antecedent* diabetes *may account* for this finding

Because ampullary cancers tend to ulcerate and *form* fistulas between the biliary and alimentary tracts the results of laboratory tests may differ *from those usually obtaining in jaundiced patients* with cancer in the head of the pancreas (Table 128)

Course Pancreatic cancer leads to death by inanition biliary obstruction local extension or *distant metastases By direct extension the cancer* may invade the liver spleen stomach duodenum colon portal venous system or peritoneum Invasion of the gut or development of varices following malignant occlusion of the portal or splenic *vein can cause moderate to severe gastrointestinal* blood loss Peritoneal seeding or very rarely portal obstruction is responsible for ascites Metastatic lesions develop in the regional lymph nodes liver lungs mediastinal and cervical lymph nodes and bones

Diagnosis In jaundiced patients differential diagnosis from liver disease or gallstones depends on the clinical picture and on laboratory tests showing in pancreatic cancer regurgitation jaundice (Chap 18) *and normal hepatic metabolic function* (Chap 18) Favoring pancreatic cancer is a gradual onset of symptoms in elderly patients without antecedent acute malaise intermittent colics or chills and fever *If itching is noticed before jaundice mechanical obstruction of the biliary passages is likely* In early cases before diagnosis is made obvious by massive or metastatic growth cancer is indicated by finding an enlarged gallbladder and a nontender *liver not more than moderately* enlarged and by not finding such stigmas of liver disease as *spider* angiomas dilated abdominal veins and splenomegaly

Radiologic procedures may show the effect of *the pancreatic lesion on other organs* Changes in the mucosa or configuration of the duodenal loop may sometimes appear as early phenomena but secondary gastrointestinal abnormalities are usually signs of advanced disease Application of newer x ray techniques such as aortograms and splenoportograms may at times prove fruitful but intravenous cholangiography will probably be most helpful in those with little icterus and on occasion *percutaneous cholangiography* via the gallbladder in those frankly jaundiced (see Chap 251)

lipemia either persistently or only during the acute attacks

Diagnosis Chronic relapsing pancreatitis is a good diagnostic possibility in all patients suffering from recurrent upper abdominal pain especially if (1) pain and tenderness extend to the left of the midline (2) alcoholism is present or gallstones and (3) more common abdominal disorders have been excluded The disease also may explain mild or recurrent jaundice diabetes or vague symptoms of indigestion particularly if these phenomena are accompanied by low grade fever or a persistently elevated sedimentation rate otherwise unexplained If pancreatic calcification is present its radiologic demonstration permits ready diagnosis but specially positioned oblique views in a patient who has not been given barium in the immediate past may be necessary to demonstrate small calcareous deposits In patients without such calcification diagnosis is best achieved by serum amylase determinations taken within 8 hr of a major attack Repeated attempts may be necessary however for the levels of amylase do not rise with each episode The bicarbonate concentration of secretin stimulated pancreatic juice is said to be reduced in 95 per cent of cases of chronic pancreatitis Absorption tests may reveal impairment of this function but it is not certain that they reveal early or mild disease of the pancreas

Treatment The consequences of pancreatic insufficiency can be controlled with moderate success by dietary restriction of fats and calories and by oral administration of 10 to 20 Gm of pancreatin daily Medical control of pain on the other hand is desultory Manipulation of diet anticholinergics and ulcer type regimens given in the hope of controlling gastric acidity and thereby lessening the stimulus for secretin production are all more or less ineffective ACTH cortisone and similar agents are of doubtful benefit and may cause harm because of their effect on gastric secretion Surgery must therefore be tried when pain is disabling but its results too are far from satisfactory Surgery is most successful if a responsible biliary tract abnormality such as stone can be corrected or if obstruction of a major pancreatic duct exists and can be eliminated by cutting a stenotic sphincter of Oddi removing an obstructing lesion near the sphincter or establishing reverse drainage by resecting the pancreatic tail with anastomosis of the severed duct to the jejunum Vagotomy subtotal gastrectomy to reduce gastric secretion and cutting a normal or spastic sphincter of Oddi to prevent biliary reflux in the pancreatic ducts have produced erratically successful results Bilateral sympathectomy and splanchnicectomy may be used as symptomatic procedures to relieve pain but the relief is only temporary in half the cases If the process is localized partial pancreatectomy may prove successful total pancreatectomy relieves pain but results in other disabilities

FIBROCYSTIC DISEASE

In this perhaps genetically transmitted disorder of infancy and childhood several organ systems are affected (1) The pancreatic acini are replaced by fibrotic tissue multiple cysts and inspissated mucus The clinical manifestations of the consequent pancreatic insufficiency are malnutrition and bulky and greasy stools (2) Somewhat similar pathologic changes affect the lungs so that the patient suffers from obstructive emphysema and is susceptible to chronic bronchopneumonia (3) The sweat and the saliva contain high concentrations of chloride and sodium in hot weather this abnormality may cause acute salt depletion and at times death (4) In a few cases the smaller hepatic biliary channels are plugged with the consequent development of cirrhosis and portal hypertension (5) In the newborn infant a thick meconium presumably viscous because pancreatic juice is absent may cause meconium ileus

The etiology is obscure One hypothesis holds that abnormally viscid mucus blocks small tubular structures in the various organs involved This concept of mucoviscidosis however does not explain the abnormalities of sweat since sweat glands secrete no mucus Diagnosis is made on the basis of the clinical picture deficiency of pancreatic ferments and high sweat electrolytes Treatment consists of pancreatic substitution therapy and antibiotics to control pulmonary infection In severe cases the prognosis is poor but patients with milder cases can survive An adult counterpart or sequel to fibrocystic disease of the pancreas is not recognized

CANCER

Incidence Cancer of the pancreas predominantly affects patients over forty five attacks men twice as frequently as women and accounts for about one out of every two to three hundred deaths It is seen about one tenth as often as gastric cancer in men and one fortieth as often as mammary cancer in women Diabetic patients are believed to have an increased susceptibility to the disease

Symptoms Weight loss pain and jaundice are the outstanding symptoms Digestive disorders including anorexia nausea loose stools or more commonly constipation are prevalent The site of the lesion however to a great extent influences the character of the symptoms their time of onset and their correct interpretation

Considering the total course of all types of pan

cystadenocarcinomas and hemangiomas Benign and malignant growths of the islet cells are discussed in Chap 69

The reader is referred to Chap 5 Acute Abdominal Pain and Ileus Chap 16 Constipation and Diarrhea Chap 18 Jaundice and Disorders of Liver Function Chap 68 Diabetes Mellitus and Chap 95 Disorders of Glycogen Storage for further consideration of problems discussed in this chapter

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Section 6 The Liver, Gallbladder, and Bile Ducts

250 DISEASES OF THE LIVER

Gerald Klatskin

In trying to establish the nature of any hepatic disorder it is helpful to begin with a consideration of the probable anatomic localization and morphologic character of the underlying lesion before proceeding to the identification of its etiology Despite the intimate interrelationships between the major functional components of the liver and the tendency for lesions in one to affect the others secondarily it is possible usually to distinguish among diseases that arise in the hepatic parenchyma biliary tree and vasculature In many instances the etiology is unknown while in others the etiology must be inferred from the character of the lesions For that reason a morphologic classification of liver disease (Table 129) is more practical than one based on etiologic factors

To avoid unnecessary duplication the clinical manifestations and functional abnormalities shared by many diseases of the liver are considered together in Chap 18 The latter is intended to serve as an introduction and should be read in conjunction with the discussion of the individual diseases in the section to follow

Table 129 CLASSIFICATION OF LIVER DISEASE

I Parenchymal
- *A* Hepatitis viral toxic associated with systemic infection granulomatous
- *B* Cirrhosis Laennec's postnecrotic biliary cardiac hemochromatosis Wilson's disease rare types
- *C* Infiltration fat iron glycogen amyloid lymphoma Gaucher's disease Niemann-Pick disease
- *D* Space-occupying lesions tumors amebic abscess pyogenic abscess gumma echinococcus cyst
- *E* Functional disorders of unknown etiology constitutional hyperbilirubinemia idiopathic icterus with pigmentation of the liver familial nonhemolytic jaundice of the newborn

II Hepatobiliary
- *A* Extrahepatic biliary obstruction stone stricture malignancy
- *B* Cholangitis

III Vascular
- *A* Chronic passive congestion
- *B* Cardiac cirrhosis
- *C* Budd Chiari syndrome
- *D* Portal vein thrombosis
- *E* Pylephlebitis
- *F* Cruveilhier Baumgarten syndrome

Table 128 CLINICAL FEATURES AND LABORATORY FINDINGS IN CANCER OF THE BILE DUCTS AND PANCREAS

	Cancer of ampulla of Vater	Cancer of bile ducts	Cancer of head of pancreas	Cancer of body and tail of pancreas
Pain	Absent—60% Moderate—40%	Absent—40% Moderate to severe—60%	Absent to mild—15% Moderate to severe—85%	Almost invariably present Agonizing and boring *Often worse in back* and accentuated when patient is supine
Jaundice				
Onset	Early	Early	Variable	Late to terminal
Character	Progressive and marked—80% Fluctuating—20%	Progressive and marked—90% Fluctuating—10%	Progressive and marked	Mild to moderate
Weight loss before onset of jaundice †	None to mild	None to moderate	Occasionally none but often 10 to 20 lb	Marked 10 to 60 lb
Fever and chills	20%	10%	None	May have low grade fever No chills
Hepatomegaly	None to slight	Slight in some cases but may be extreme	Moderate Marked only if metastases present	None to marked Size depends on degree of metastatic involvement
Enlarged gallbladder palpable or visible	50%	20%	50%	0
Splenomegaly	None	None	None	Occasional
Bile in stools and urobilinogen in urine	Absent—80% Fluctuating—20%	Absent—90% Fluctuating—10%	Absent	Present
Occult blood in stool	50%	15%	Rare	Rare

* Because of their anatomic proximity advanced cancers of the ampulla of Vater the bile ducts and the pancreatic head at times cannot be distinguished clinically

† All these cancers cause impressive weight loss sooner or later

When the patient is not jaundiced early diagnosis is difficult particularly since the patient may exhibit psychoneurotic tendencies Persistent pain and progressive weight loss with negative radiologic studies of the alimentary renal and biliary passages should raise the suspicion of pancreatic cancer In *patients with ascites the character of the fluid and* its cellular content often permit the diagnosis of cancer but differential diagnosis from ovarian gastric or primary hepatic cancer is not easy Duodenal drainage may reveal neoplastic cells in the cellular sediment

Treatment Resection of lesions confined to the ampullary area is successful in terms of 5 year cures in 15 per cent of the cases In cancers located elsewhere in the pancreas extensive pancreatic duodenal resection including total pancreatectomy is feasible in many instances but the patient almost invariably succumbs *to local or distant recurrence* In jaundiced patients however palliative anastomosis of the gallbladder to the intestinal tract affords relief from the intolerable itching Before operation is undertaken any existing deficiencies of water electrolytes red cells and vitamin K should be corrected

OTHER CONDITIONS

The pancreas is often involved by mumps but only rarely is pancreatitis the sole manifestation of the disease Like other viscera the pancreas may be affected by periarteritis nodosa

Ectopically placed pancreatic tissue may be found in the gastrointestinal tract Meckel's diverticulum and various other areas Nearly all pancreatic rests radiologically discovered in adult however occur in the distal stomach and duodenum Rarely the rest creates an annular constriction of the duodenum

Unusual pancreatic neoplasms are cystadenomas

tion accounts for the infrequency with which definite exposure to the disease can be established Young children and especially infants appear to be an important reservoir for this type of infection Explosive epidemics may follow exposure to feces contaminated water or food supplies and occasionally infections are acquired by the parenteral route following the transfusion of blood or the use of blood contaminated instruments In many areas infections are more prevalent in the autumn and early winter months but in others there appears to be no seasonal fluctuation

The disease may occur at any age but is most common in children and young adults After the age of thirty the incidence is relatively low apparently because of immunity acquired in early life No doubt this accounts also for the effectiveness of pooled gamma globulin in preventing infection following exposure The immunity that follows infection is usually lifelong in duration but may be less sustained in some individuals so that reinfection is possible

In SH virus infections the virus gains entry to the body by the parenteral route as a result of transfusions or injections of infected blood plasma or serum or the use of improperly sterilized blood contaminated needles syringes or other surgical equipment Occasionally handlers of blood and blood products become infected presumably through nicks in the skin The disease may occur also following the use of topical thrombin However other blood products prepared by the ethanol fractionation method such as gamma globulin serum albumin and antihemophilic globulin appear to be noninfectious Recent evidence suggests that the transplacental transmission of virus to the fetus in pregnant asymptomatic carriers may be responsible for neonatal hepatitis and that this may be an important mode of propagating the virus from one generation to the next

Asymptomatic carriers play a key role in the spread of this disease Estimates of their prevalence are not available but on the basis of the number of infections that follow a single blood transfusion they would appear to comprise approximately 1 per cent of the population Very few of these individuals have had a clinically recognizable infection but some exhibit minor alterations in liver function and a few have significant hepatic lesions suggesting that some carriers at least have active but subclinical disease

Since a large number of bloods is used to make up a single pool of plasma the recipient of a plasma infusion is exposed to numerous potentially infected donors As a result the risk is very much greater than that following a single blood transfusion. The virus may be present in high concentration. In some instances as little as 0 00005 ml is infectious which explains why needles syringes and other instruments inconspicuously contaminated with blood may serve as vehicles for infection

Pathology

The lesions of viral hepatitis which are uniformly distributed throughout the liver are characterized by degeneration and necrosis of parenchymal cells proliferation and swelling of the reticuloendothelium and cellular infiltration of the sinusoids and portal triads Scattered groups of hepatic cells undergo rapid lysis especially in the pericentral areas of the lobules while many of the remaining cells show degenerative changes characterized by ballooning or hyalinization to form densely stained acidophilic bodies Almost from the beginning there are signs of active regeneration including mitotic figures hyperchromatism and numerous binucleate cells As a result of these changes the liver cords are disrupted and distorted leading to disorganization of the normal lobular pattern The intervening sinusoids contain clumps of swollen Kupffer cells and numerous lymphocytes plasma cells wandering macrophages and occasional eosinophils and polymorphonuclear cells A similar exudate is seen in the portal triads Many of the macrophages adjacent to necrotic areas contain lipofuscin a yellow acid fast pigment presumably derived from broken down hepatic cells Occasionally some of the canaliculi are filled with inspissated bile

The reticulum fibers are spared and serve an important function in providing a framework for the orderly reorganization of the lobules As long as the areas of necrosis whatever their size are limited to the confines of the individual lobules local regeneration and restitution of the normal architecture are assured In contrast when the necrotic zones encompass whole lobules this is not possible since regeneration must proceed from distant unaffected lobules This leads to the formation of large regenerating nodules which compress the intervening reticulum of the completely destroyed lobules into bands containing the remaining blood vessels regenerating ducts and exudate This variant of the disease is known as subacute necrosis of the liver Ultimately if the patient survives the collapsed reticulum undergoes collagenization, giving rise to postnecrotic cirrhosis However even in the healed state signs of varying degrees of active parenchymal inflammation and necrosis may be evident for long periods of time When the areas of necrosis are extensive the liver tends to be small and coarsely nodular with broad intervening bands of collapse and fibrosis the usual picture in this type of cirrhosis However if the necrosis involves limited numbers of adjacent lobules a finely nodular cirrhosis may ensue Fine nodulation may occur also as a result of progressive degeneration

PARENCHYMAL

Hepatitis

Viral Hepatitis

Viral hepatitis is an acute systemic infection that affects the liver predominantly giving rise to highly characteristic hepatic lesions The disease occurs in two forms due to closely related but distinct etiologic agents known as *virus IH* and *SH* or *A* and *B* respectively The two infections are indistinguishable on the basis of their clinical and morphologic manifestations but they exhibit differences in their epidemiologic and immunologic behavior The IH type is known as *infectious* or *epidemic hepatitis* the SH type as *homologous serum posttransfusion inoculation* or *syringe transmitted hepatitis* Since both viruses may be transmitted by the parenteral route the terms indicated may be confusing There is a growing tendency therefore to supplant them with the terms IH and SH or A and B viral hepatitis Before the pathogenesis of viral hepatitis was understood the IH type was called *catarrhal jaundice* in the mistaken belief that the symptoms were due to an inflammatory obstruction of the common duct There is no justification for the continued use of this obsolete term

Etiology

The agents responsible for this form of hepatitis have not been identified microscopically or serologically and have not been propagated in tissue culture embryonated eggs or experimental animals However they have been shown to be filtrable through a Seitz EK filter and are readily transmitted to susceptible human volunteers suggesting very strongly that they are viral in nature What little is known about the properties and behavior of these viruses has been derived from transmission experiments in man Since of necessity these experiments have been limited in number there are still a great many gaps in knowledge of the viruses The absence of a susceptible animal host or a suitable serologic technique for identifying these agents has been a stumbling block in the study of viral hepatitis not only for the virologist but also for the clinician pathologist and epidemiologist From a diagnostic point of view the clinician is obliged to depend on clinical and laboratory features which while highly characteristic are never pathognomonic Even the histologic changes in the liver which are more specific cannot be considered unequivocal evidence of infection particularly in the more unusual and late forms of the disease in which the morphologic features are less distinctive

Both the IH and SH viruses are peculiarly resistant to heat (56 C for 30 min and 60 min respectively) prolonged storage in the cold (−10 to −20 C for 1½ and 4½ years respectively) and the action of chemical agents (chlorine 1 1 000 000 for the IH virus and merthiolate 1 2 000 tricresol 2 1 000 and equal parts of phenol and ether 5 1 000 for the SH virus)

The principal differences between the two viruses may be summarized as follows (1) the IH virus has been recovered from both blood and feces the SH virus from the blood only (2) the IH virus may be transmitted to man by either the oral or the parenteral route the SH virus by the parenteral route only (3) the incubation period is 2 to 6 weeks for the IH virus irrespective of the route of administration and from 6 weeks to 6 months for the SH virus (4) the IH virus has been found in the blood from 3 days before to 8 days after the onset of jaundice while the SH virus has been recovered at intervals throughout the long incubation period and during the acute phase of the disease with the rare exceptions to be mentioned in neither case has the agent been demonstrated during convalescence (5) the asymptomatic carrier state appears to be more common and prolonged in the SH type virus having been demonstrated in the blood for periods up to 5 years in individuals with no history of hepatitis the IH type has been recovered from the feces during convalescence in only two instances 4 and 15 months following infection but never from blood or feces in individuals with no history of hepatitis (6) both viruses confer homologous but not heterologous immunity (7) gamma globulin isolated from large pools of plasma collected from randomly selected donors protect against IH but not against SH infection (8) IH infections occur at an earlier age tend to be less severe and are more likely to be accompanied by preicteric constitutional symptoms

It is still not clear whether these two types of virus represent distinct species or merely strain variants of the same species Moreover it is not known whether all the strains belonging to each type are antigenically identical Clinical and epidemiologic studies and transmission experiments have failed to demonstrate any significant differences between the behavior of the strains of each type isolated in various areas of the world However more precise information will have to await the development of better methods of isolating and identifying these agents

Epidemiology

IH viral hepatitis occurs both sporadically and in epidemic form The latter is seen particularly under conditions of crowding and poor sanitation Infection is usually acquired through the oral route by close personal contact with individuals passing virus in their feces It is presumed that the occurrence of many unapparent infections in the popula

Characteristically the jaundice increases rapidly reaching a maximum in 3 to 14 days and then recedes at a somewhat slower rate clearing up completely in 1 to 6 weeks If the serum bilirubin level is followed closely it can be shown that in typical cases there is no plateau at the peak although one may occur during convalescence as the serum bilirubin approaches the normal concentration The intensity of the jaundice at its maximum tends to mirror the extent of the hepatic damage so that usually it provides some indication of the expected severity and duration of the disease However there are many exceptions minimal jaundice therefore does not exclude the possibility of severe hepatic injury nor does deep jaundice necessarily imply a protracted or severe illness

Immediately following the subsidence of jaundice the patient usually feels well but recovery is seldom complete at this stage The liver may be enlarged and tender abnormalities of hepatic function are often evident and histologic studies usually show incomplete resolution of the lesion Of even greater importance resumption of full activity at this time may precipitate a relapse with a recrudescence of any or all of the previous symptoms The duration of this *posticteric phase* varies from 2 to 6 weeks but may be longer in some instances However full clinical and biochemical recovery is to be expected within 4 months

Laboratory Features The *leukocyte count* is normal but may be low during the preicteric phase Occasionally atypical lymphocytes indistinguishable from those of infectious mononucleosis are present in small numbers The *sedimentation rate* is high in the preicteric stage falls to normal during the icteric stage and rises again during convalescence

The *urine* may contain traces of bilirubin even before jaundice appears As jaundice deepens the amount of bilirubin increases but during convalescence bilirubin excretion often ceases before the serum bilirubin has returned to normal During the preicteric phase urine urobilinogen may be increased but as jaundice and light colored feces appear the amount of urobilinogen falls to the normal level Often a secondary increase in urine urobilinogen occurs when the jaundice begins to fade and the stools return to their normal color Finally the level falls to normal when recovery has occurred

Early in the course of the jaundice the stools may be light or clay-colored for a few days to a week Later their appearance is normal In many cases there is no change in color despite the presence of overt jaundice

The *direct and total serum bilirubin* levels rise and fall together and reflect the depth of jaundice The direct fraction usually constitutes 50 to 75 per cent of the total early in the course of the disease but may be relatively lower later An increase in the direct fraction without a concomitant rise in the total bilirubin may be seen both in the preicteric phase and late in convalescence In a few individuals the indirect fraction remains slightly elevated for long periods following apparent recovery

Bromsulphalein retention is increased during the preicteric phase and remains so for some time after the subsidence of jaundice It returns to normal when healing is complete but occasionally mild retention persists despite apparent full recovery

The *cephalin cholesterol flocculation* and *thymol turbidity* tests usually become positive toward the end of the preicteric phase or shortly thereafter They tend to revert to normal late in convalescence but often persist for long periods following apparent recovery Occasionally one or both tests remain normal throughout the course of the disease

The *serum alkaline phosphatase* level tends to rise slightly but occasionally it reaches the concentration seen in extrahepatic obstructive jaundice

The *serum protein pattern* is normal early in the disease but may show a fall in albumin and a rise in globulin if the disease is prolonged or severe

Usually the *serum cholesterol concentration* is normal but during the icteric phase the percentage of esters tends to fall In a few individuals a high total cholesterol is seen transiently during the phase of increasing jaundice

Diagnosis During the preicteric phase viral hepatitis may be difficult to differentiate from a number of other infections but marked anorexia out of proportion to the degree of fever subcostal tenderness and the occurrence of dark urine should alert the clinician to the possibility of viral hepatitis and call for investigation of the liver by appropriate tests

Once jaundice has appeared it becomes necessary to exclude other forms of hepatitis an exacerbation of a chronic hepatic disorder and extrahepatic biliary obstruction A careful history will usually suffice to rule out toxic and drug hepatitis but the appearance of renal failure or signs of a hypersensitivity reaction should call for further inquiry Marked myalgia nuchal rigidity conjunctival injection and leukocytosis should suggest the possibility of leptospirosis A severe sore throat and marked cervical adenopathy may be indicative of infectious mononucleosis with jaundice The presence of spider nevi ascites or edema early in the disease usually denotes an underlying cirrhosis but later it may be indicative of subacute necrosis of the liver Shaking chills colicky pain significant leukocytosis and a past history of dyspepsia usually point to a common duct stone

Even in the most typical case of viral hepatitis

and collapse of large nodules because of either continued inflammatory activity or the tendency of the nodules to outgrow their circulatory supply At this stage it may be difficult to distinguish the lesion from that of Laennec s cirrhosis

Occasionally the hepatitis virus produces *massive necrosis of the liver* In this condition there are large areas of necrosis and collapse as in subacute necrosis but death ensues before signs of regeneration appear Since the liver tends to shrink in size and is often bile stained at least early in the disease the lesion was once termed *acute yellow atrophy*

It should be noted that while the hepatitis virus is the most common cause of subacute and massive necrosis certain drugs and poisons are capable of producing a very similar lesion

Although restoration of the normal architecture and resolution of the inflammatory reaction are the rule following recovery from *uncomplicated* viral hepatitis mild degrees of periportal fibrosis and round cell infiltration are common residuals They bear no relationship to the minor symptoms and alteration in function that may be present at this time and are *not* to be interpreted as evidence of chronic hepatitis

Clinical Manifestations

Usually the clinical manifestations follow a highly characteristic pattern and subside without residuals within a period of 4 months For purposes of identification and further discussion this form of the disease will be designated as *typical acute viral hepatitis* In approximately 15 per cent of patients the clinical course is atypical in that it terminates fatally is greatly prolonged or is characterized by unusual manifestations These features are sometimes considered complications of the disease but it should be emphasized that the basic lesion is the same in all instances

The mortality rate based usually on the number of fatalities from subacute and massive necrosis that occur within the first few months of the disease is said to lie between 0 2 and 0 4 per cent This does not take into account the late deaths that follow residual postnecrotic cirrhosis However since the number of unrecognized mild and non icteric infections is probably large the over all mortality rate may be considerably lower than that indicated

Little is known about the factors responsible for the variations in the severity and clinical course of viral hepatitis Complicating malnutrition alcoholism intercurrent infection physical exhaustion and inadequate therapy are thought to be important but the evidence implicating these factors is inconclusive The severity of the disease and its mortality rate appear to be greater in older persons and in those infected with the SH virus possibly because of the higher incidence of complicating disease in such individuals

Typical Acute Viral Hepatitis

Symptoms and Signs In approximately 80 per cent of IH but in only 20 per cent of SH viral infections the onset of jaundice is preceded by a period of nonspecific constitutional and gastrointestinal symptoms that may last from a few days up to 2 weeks Often these symptoms are mistaken for signs of a respiratory infection or acute gastroenteritis

Usually the onset of the *preicteric phase* is abrupt *Fever* marked *anorexia* and *weakness* are the outstanding symptoms and often a sudden distaste for cigarettes is a striking feature These symptoms may be accompanied by nausea and vomiting indigestion abdominal pain headache pain on moving the eyes arthralgia and myalgia Occasionally there is an erythematous or urticarial rash As a rule the fever is remittent and only moderate in degree but in severe infections it may be high and associated with marked prostration Chilly sensations are relatively common in such cases but *frank shaking chills are rare* When abdominal pain is present it is usually dull and aching in character and located in the epigastric area or right upper quadrant Rarely it is severe and may be accompanied by marked abdominal tenderness and spasm suggesting an acute surgical emergency In some individuals upper respiratory symptoms are a prominent feature

Often at this stage the liver is slightly enlarged and tender but even if it is not percussion over the hepatic region may provoke pain In about 20 per cent of patients a mild degree of splenomegaly can be demonstrated and in a somewhat smaller number the posterior cervical lymph nodes are enlarged

Within a few days to a week of the onset and sometimes even before the appearance of jaundice the urine darkens owing to the presence of bilirubin This may be the first clue to the true nature of an otherwise obscure febrile illness Usually icterus of the skin and sclerae becomes evident within a day or two

Early in the *icteric phase* the jaundice deepens hepatic enlargement and tenderness become more evident and the patient s general condition worsens However within a few days the fever and preicteric symptoms usually abate even though the icterus is still increasing Occasionally the fall in temperature and clinical improvement coincide with the appearance of clinical jaundice but in severely ill patients prostration anorexia nausea and vomiting may persist or even increase after subsidence of the fever Unless measures are taken to maintain food intake marked weight loss may ensue

coma Not infrequently the serum albumin falls and the globulin increases. When the clinical course is prolonged, hyperglobulinemia may be extreme As hepatocellular function fails the serum cholesterol may fall to abnormally low levels.

Terminally the patient lapses into hepatic coma and dies of advanced hepatocellular failure How ever in patients with a prolonged course death may be due to intercurrent infection or massive bleeding from esophageal varices

"Cholangiolitic" Hepatitis Occasionally patients with a typical onset of acute viral hepatitis develop clinical and laboratory features suggestive of biliary obstruction. It has been postulated that the inflammatory reaction in such cases involves the terminal perilobular cholangioles permitting the regurgitation of bile as a result of compression by exudate or abnormal permeability For that reason the syndrome has been called *cholangiolitic* hepatitis However there is no histologic evidence that the cholangiolar involvement is any more severe or qualitatively different from that in the usual form of hepatitis so that the theory of increased cholangiolar permeability or obstruction rests solely on circumstantial clinical evidence Most pathologists do not consider "cholangiolitic" hepatitis a distinct pathologic entity but the unusual clinical manifestations of the syndrome warrant its classification as an atypical variant of acute viral hepatitis

The distinctive features of the disease are prolonged jaundice often accompanied by pruritus significant hepatomegaly a sustained and marked increase in the percentage of direct reacting serum bilirubin, high levels of serum alkaline phosphatase and cholesterol, and a negative or only weakly positive cephalin-cholesterol flocculation reaction Usually the serum albumin concentration is normal or only slightly depressed but the globulin fraction is almost always increased Early in the disease the histologic features are indistinguishable from those of typical acute viral hepatitis but later they may be difficult to differentiate from those of an extrahepatic biliary obstruction the principal findings being bile staining of the parenchyma intracanalicular bile thrombi and a mononuclear periportal exudate without hepatocellular changes

Except for unusual fatigability and pruritus the patient often feels remarkably well and goes on to an uneventful recovery after a period of sustained or fluctuating jaundice lasting from a few months to a year In some instances however the disease appears to be progressive giving rise to cholangiolitic cirrhosis an entity thought to be closely related to primary biliary cirrhosis (p 1508)

The differentiation between cholangiolitic hepatitis and extrahepatic biliary obstruction may be exceedingly difficult even after the most exhaustive investigation including liver biopsy so that exploratory laparotomy may be necessary However a careful history will often reveal the typical symptoms of viral hepatitis at the onset, and the results of liver function tests carried out early in the course of the disease are likely to be more typical of hepatocellular disease Certain drugs and particularly chlorpromazine (Thorazine) and methyltestosterone are capable of producing an identical picture It is essential, therefore that the possibility of a drug reaction be excluded with certainty in all instances of suspected "cholangiolitic" hepatitis.

Sequelae

Occasionally signs or symptoms of liver disease persist or recur beyond the 4-month period during which recovery is to be expected. This may be because of slow resolution and healing, progressive inflammation and destruction of the parenchyma, postnecrotic scarring functional disorders of the parenchyma, or even complicating psychogenic disturbances. It is misleading therefore to classify all forms of delayed recovery as "chronic viral hepatitis Moreover the term has the additional disadvantage that it is sometimes used in a more specific sense to indicate posthepatitic cirrhosis or chronic parenchymal destruction leading to cirrhosis Wherever possible an attempt should be made to determine the anatomic and physiologic basis for the persistence of abnormal findings. Unfortunately this is not always feasible without resort to liver biopsy but prolonged observation and serial laboratory studies often suffice to distinguish between the several types of prolonged or recurrent hepatitis to be discussed

Minor Residuals without Clinical Significance A significant number of patients with acute viral hepatitis exhibit minor abnormalities of hepatic function or slight nontender hepatomegaly for periods of several months to a year following apparent clinical recovery Slight increases in thymol turbidity and cephalin cholesterol flocculation are the most common findings but serum bilirubin levels of 1.2 to 2 mg per 100 ml and Bromsulphalein retention of 6 to 10 per cent are not rare Liver biopsy in this group invariably reveals complete healing It should be noted however that both in this group and in patients without residuals the portal triads may show a mild degree of fibrosis and mononuclear cellular infiltration. In the absence of parenchymal changes there is no evidence that either the histologic or functional residuals described are forerunners of progressive disease or relapse

Prolonged Convalescence In this group any or all of the clinical or laboratory features of the acute disease may persist for long periods, but usually full recovery ensues within a year On histologic examination the liver shows incomplete healing of the parenchymal lesions as in the convalescent

the clinical course should be scrutinized with care since any deviation from the usual pattern may indicate an error in diagnosis or the occurrence of a complication The particular points to note are the duration of the preicteric phase the time it takes for jaundice to reach its maximum the presence or absence of a plateau at the peak of the serum bilirubin curve and the occurrence of ascites edema or spider nevi

Variants of Acute Viral Hepatitis

Acute Anicteric Hepatitis A number of individuals infected with the hepatitis virus fail to develop jaundice In some patients the clinical features are otherwise identical with those of the icteric form of the disease although they tend to be somewhat milder However there is reason to believe on the basis of transmission experiments that the disease may present as a nonspecific illness without localizing signs In infants and young children a mild gastroenteritis or diarrhea may be the only manifestation Liver function tests may show the same pattern seen in icteric hepatitis but often the changes are less striking Occasionally the direct and total serum bilirubin levels are slightly elevated and traces of bile can be demonstrated in the urine

Diagnosis is difficult in this group unless an epidemic is in progress or the clinical and laboratory features closely resemble those of the icteric form of the disease Under other conditions the diagnosis can seldom be made with confidence since the symptoms and changes in liver function are nonspecific

The high incidence of immunity to IH virus infections in adults with no history of hepatitis suggests that anicteric infections are common However relatively few are recognized clinically

Fulminant Hepatitis (Massive Necrosis of the Liver) This form of the disease is usually fatal within 10 days some deaths occurring as early as the second day In the preicteric and early icteric phases the clinical and laboratory features may be identical with those in the more benign type However nausea vomiting and abdominal pain tend to be more severe and jaundice is likely to appear earlier and to deepen more rapidly Usually the first clue of an impending fatal outcome is the appearance of cerebral manifestations indicating the onset of hepatic coma Occasionally the disease is ushered in with neurologic manifestations and progresses rapidly to deep coma and death Other features seen in many but not all cases include a sharp terminal rise in temperature significant leukocytosis a rapid decrease in the size of the liver coffee grounds vomitus or gross hemorrhage into the gastrointestinal tract purpura and ascites Terminally the patient lapses into deep coma and may exhibit muscular twitchings convulsions shock oliguria and azotemia Occasionally the course of the disease is so rapid that death occurs before jaundice develops It may be difficult to establish the diagnosis in such cases unless the possibility of viral hepatitis is considered and appropriate laboratory studies are carried out

Subacute Hepatitis (Subacute Necrosis of the Liver) The clinical course in subacute necrosis of the liver varies depending on the extent of the necrosis the degree of healing and the amount of regeneration As in the fulminant form of the disease the illness often begins as an uncomplicated viral hepatitis only to go on to progressive hepatic failure and death Many patients die within 2 to 12 weeks but some survive for a period of a year or more and a few go on to apparent clinical recovery In the latter group postnecrotic scarring and cirrhosis are inevitable but the outcome depends on the activity of the associated parenchymal inflammatory process and the degree of portal hypertension that develops Relapses with jaundice and other signs of hepatic failure are common in those with active inflammatory lesions and may terminate fatally after one or more such episodes Not infrequently the first recognizable signs of subacute necrosis of the liver make their appearance during a relapse following what was believed to be an uncomplicated attack of acute viral hepatitis There is reason to believe that the apparent progression in such cases merely represents the recrudescence of a lesion incurred during the initial infection Occasionally the same picture is seen following an attack of anicteric hepatitis In cases with postnecrotic scarring there may be a long asymptomatic interval between the initial infection and the accidental discovery of cirrhosis or the occurrence of bleeding from esophageal varices Biopsy studies of the liver indicate that mild forms of subacute necrosis and postnecrotic fibrosis occur more frequently than is evident clinically It is possible therefore that viral hepatitis may be responsible for many instances of cirrhosis discovered years after the initial infection

The clinical features that should suggest the possibility of subacute hepatic necrosis in patients with acute viral hepatitis include (1) jaundice that increases progressively for more than 2 weeks remains stationary at a high level or shows recurrent remissions and relapses (2) fever and leukocytosis that appear after jaundice has developed (3) ascites edema and numerous large spider nevi (4) the appearance of splenomegaly late in the course of the disease (5) severe and persistent vomiting particularly if accompanied by coffee grounds vomitus (6) severe abdominal pain (7) a hemorrhagic tendency as evidenced by epistaxis hematemesis melena hematuria or purpura and (8) fetor hepaticus and other signs of impending

derived from bed rest in the more prolonged forms of viral hepatitis An attempt should be made therefore to determine when maximum benefit has been achieved This can be accomplished by delaying ambulation until the levels of serum bilirubin and Bromsulphalein retention have been stable for at least a week The patient is then allowed increasing activity under supervision If there is any tendency for the clinical signs or laboratory abnormalities to worsen bed rest should be resumed

Diet Patients with viral hepatitis may lose considerable weight If this is prevented by feeding sufficient calories convalescence may be shortened *An intake of 2500 to 3000 cal* is usually adequate but this may be difficult to achieve for short periods during the acute phase of the disease particularly if parenteral feeding becomes necessary

The *optimal protein requirement* is still a matter of debate Many including the author believe that positive nitrogen balance can be achieved with an intake of 70 to 100 Gm and that the regenerative rate of the liver cannot be accelerated by providing an excess However in the military study previously mentioned an intake of 150 to 200 Gm appeared to shorten the period of convalescence significantly but these results are difficult to reconcile with those previously reported by others Except in patients with subacute or massive hepatic necrosis and impending coma in whom the protein intake must be sharply curtailed there is no harm in forcing protein to this extreme but it is difficult to do so and the physician need not be alarmed if he fails

The *fat content* of the diet need not be limited There is no evidence that fats are harmful and indeed, they are useful in enriching the caloric value and palatability of the diet However while milk butter and eggs are usually well tolerated fried and cooked fats often produce gastrointestinal distress and therefore should be restricted

Once the protein requirement has been satisfied and fat has been added as tolerated the remaining caloric needs are made up with *carbohydrate* A high carbohydrate intake has no special virtue and the outmoded practice of forcing sweets throughout the day is to be condemned since it often spoils the patient s appetite for other foods and may provoke fatty infiltration of the liver if the patient s protein intake is not increased proportionately

There is no convincing evidence to show that vitamin supplements are of value in the treatment of viral hepatitis although they may be indicated if there was antecedent malnutrition or if prolonged parenteral feeding becomes necessary Similarly there is no logical reason for adding lipotropic substances like choline and methionine to a balanced diet particularly since fatty infiltration is not a feature of viral hepatitis

Severe anorexia, nausea and vomiting may necessitate resort to parenteral feeding A slow drip of 15 per cent glucose providing from 300 to 400 Gm per day will usually suffice to maintain the patient in a reasonable state of nutrition and hydration over the brief period usually required before oral feedings can be resumed The amount of sodium potassium and chloride to be added to the solution will depend on the losses in the urine feces vomitus and sweat and may be estimated from the state of hydration and the serum electrolyte pattern Parenteral amino acid supplements have been advocated but there is no evidence that they are of special benefit Moreover they frequently cause reactions and are contraindicated in patients with impending coma

Antibiotics The antibiotics do not appear to be of any value in the treatment of acute viral hepatitis However broad spectrum antibiotics may be useful in the management of coma complicating massive and subacute hepatic necrosis Also it has been reported that chlortetracycline (Aureomycin) hastens recovery in patients with prolonged convalescence although the evidence for this is not very convincing

ACTH and Cortisone These agents are capable of inducing a prompt clinical remission in acute viral hepatitis However the length of the convalescent period is not shortened in the uncomplicated form of the disease and relapses are common unless treatment is prolonged It is deemed inadvisable therefore to subject patients to the possible hazards of ACTH and cortisone therapy unless there are clear cut indications for it. Certainly this form of treatment is warranted when the symptoms are severe and do not respond to conservative measures and when there are signs of subacute hepatic necrosis There is a clinical impression that the duration of the disease is shortened and that residual lesions are minimized under these conditions but the evidence for this is still inconclusive Not infrequently a course of steroid therapy is effective in terminating prolonged convalescence particularly in patients with chronic "cholangiolitic" hepatitis and occasionally large doses appear to be lifesaving in comatose patients with massive hepatic necrosis Although it is worth trying these agents in the treatment of postnecrotic cirrhosis with evidence of active inflammatory disease the results are usually disappointing and complications are frequent

In using ACTH and cortisone treatment should be continued until the serum bilirubin drops to a normal level or reaches a stable plateau but in either event for a period of not less than 3 weeks In acutely ill patients an infusion of 25 units of ACTH daily administered over an 8- to 10-hr period appears to yield the most satisfactory results although intramuscular cortisone acetate in doses of

stage of the uncomplicated form of the disease In the writer's experience this lesion shows no tendency to progress to subacute necrosis of the liver or to posthepatitic cirrhosis However it is in this group that recrudescences may occur either spontaneously or following premature return to full activity

Subacute Hepatic Necrosis and Posthepatitic Cirrhosis Before signs of overt hepatic failure or portal hypertension appear it may be impossible to distinguish between the clinical and laboratory manifestations of persistent liver disease due to subacute hepatic necrosis and posthepatitic cirrhosis and those due to prolonged convalescence from the uncomplicated form of viral hepatitis However the two can be differentiated readily on the basis of their histologic features

Relapses and Recurrence Not infrequently there is a transient recurrence of symptoms or an increase in functional abnormalities during convalescence Usually this is the result of premature ambulation and resumption of full activity but it may occur also without provocation The manifestations may be identical with those of the initial attack or even more severe but usually they are milder and of shorter duration When the interval between the two attacks is less than 6 months the recurrence almost invariably represents a recrudescence of an unrecognized incompletely healed lesion of either the prolonged convalescent or subacute necrotic type The possibility of reinfection with the heterologous strain of the hepatitis virus or of an error in diagnosis must be considered when the interval is longer However the relapses in posthepatitic cirrhosis which may resemble those of acute hepatitis often occur at long intervals

Posthepatitis Syndrome Occasionally patients complain of unusual fatigability vague discomfort in the right upper quadrant anorexia and indigestion for long periods following complete subsidence of all clinical laboratory and histologic evidence of active liver disease Psychogenic factors are thought to be responsible for this syndrome However in the writer's experience the syndrome is rare in individuals who have had adequate bed rest during convalescence which suggests that it may represent a type of postinfectional asthenia

The Carrier State The importance of carriers in the spread of viral hepatitis has been touched on under Epidemiology Only rarely does the carrier state follow a clinically recognizable attack of acute viral hepatitis which suggests that it is usually the result of an asymptomatic infection However in a few instances virus has been recovered from the feces of infants convalescing from a prolonged but mild illness Since parenteral injections can hardly account for the unusually large number of SH virus carriers in the population serious consideration must be given to the suggestion that the virus may be acquired transplacentally before birth The question of whether the carrier harbors the virus in a diseased liver or merely permits its propagation without incurring any hepatic injury is still under study A significant number of carriers show minor abnormalities of hepatic function and in a few significant histologic changes have been demonstrated in the liver However many carriers show no clinical chemical or histologic evidence of liver disease

Treatment

Rest It is the opinion of many that strict bed rest is indicated until the signs of active hepatic disease have subsided However on the basis of a recent experimental study carried out under carefully controlled conditions in military personnel it has been recommended that patients be allowed up as soon as the acute symptoms abate and that further physical activity be limited to the confines of a hospital ward until full recovery ensues It is difficult to reconcile the results of this investigation with the experience of most clinicians indicating that the incidence of recrudescences prolonged convalescence and postinfectional asthenia is significantly reduced by enforced bed rest Until this difference of opinion is resolved the clinician would be well advised to err on the side of conservatism particularly since complete bed rest does not entail any greater loss of time from work than limiting activity to the confines of the patient's home or hospital ward Moreover the increase in the length of time required for recuperation following a regime of strict bed rest reported in military personnel has not been observed in civilian patients

The patient may be allowed out of bed when (1) all symptoms have subsided (2) the liver is no longer significantly enlarged or tender and (3) the levels of total serum bilirubin and Bromsulphalein retention have fallen below 2 mg per 100 ml and 10 per cent respectively Residual abnormalities in cephalin cholesterol flocculation and thymol turbidity may be disregarded Activity should be increased slowly and a close watch kept for signs of clinical or laboratory relapse If these signs appear bed rest should be reinstituted Resumption of full activity is permitted when the patient's strength has returned to normal In those with residual hepatomegaly or minor alterations in liver function further follow up studies at monthly intervals are advisable The physician should exercise great care in reassuring the patient that such studies are a precautionary measure and that most minor residuals have no clinical significance For that reason it is unwise and usually unnecessary to limit the patient's activity or diet during this period

Obviously there are limits to the benefits to be

vating essential protoplasmic enzyme systems In contrast most drugs that produce hepatic injury such as cinchophen and the sulfonamides exert their effects by inducing a hypersensitivity reaction However a few like chloroform are truly hepatotoxic while others such as the arsenicals may behave both as hepatotoxins and sensitizing agents A number of parenterally administered drugs once considered hepatotoxic because of their apparent tendency to produce jaundice are now known to serve as innocuous vehicles in the transmission of the hepatitis virus by means of inadequately sterilized blood contaminated syringes The type of hepatitis that accompanies certain systemic infections and metabolic disturbances is thought to be the consequence of an endogenous intoxication However little is known about the nature of the presumed toxins involved or the manner in which they exert their deleterious effects so that this form of hepatitis will be considered separately

Local circulatory disturbances and hypoxia may be important contributory factors in the pathogenesis of toxic hepatitis In addition the nutritional status the synergistic effects of alcohol and infection the presence of preexisting liver disease and differences in individual susceptibility may modify the actions of hepatotoxins and sensitizing agents According to some authorities hepatotoxins exert their deleterious effects on the liver by inducing a specific deficiency of essential nutriments such as cystine However there is little convincing evidence that this is a factor in any of the forms of toxic hepatitis seen in man

The clinical and pathologic features of the hepatitis produced by hepatotoxins and sensitizing agents are sufficiently different to warrant their consideration as separate entities Since space does not permit a detailed discussion of the individual agents in each group Table 130 is appended at the end of this chapter to indicate their probable mode of action Accidental transmission of the hepatitis virus while not a factor in the pathogenesis of toxic hepatitis is included since its importance in many forms of drug induced hepatitis is often overlooked Obviously any parenterally administered drug may serve as a vehicle for the hepatitis virus but only those which have been implicated frequently or have been erroneously considered hepatotoxins are indicated in the table

Toxipathic Hepatitis Characteristically the liver lesions produced by true hepatotoxins make their appearance within a day or two of exposure are readily reproducible in most if not all species and exhibit morphologic features distinctive for each of the agents In many instances there are accompanying toxic lesions in other organs especially in the kidney

The *histologic changes* in the liver vary not only with the agent involved but also with the dose and route of administration In general however the acute lesions tend to be distributed uniformly throughout the lobules in either a central or a periportal zonal pattern and they show all stages of parenchymal degeneration from simple swelling to acute necrosis with little or no inflammatory reaction Often fatty infiltration is a prominent feature Usually the lesion is reversible but death may occur before healing takes place Some poisons such as the *Amanita phalloides* toxin and the chlorinated naphthalenes produce subacute and massive hepatic necrosis which if not fatal leads to the development of postnecrotic cirrhosis Even the agents that produce reversible lesions such as carbon tetrachloride may give rise to cirrhosis if the exposures are repeated at close enough intervals to prevent normal healing

Usually the *clinical picture* resembles that of acute viral hepatitis except for the absence of preicteric fever and constitutional symptoms Anorexia nausea and vomiting are the principal symptoms while jaundice and hepatomegaly are the major physical findings It should be noted however that significant liver damage may occur without producing jaundice The *laboratory features* also are similar to those in viral hepatitis although the changes in cephalin cholesterol flocculation and thymol turbidity tend to be less striking

In addition to the symptoms of liver injury there may be others referable to the extrahepatic pharmacologic and toxic effects of the offending agent Often it is difficult to distinguish between these two groups but renal failure and severe gastrointestinal irritation usually are due to extrahepatic lesions

As a rule recovery occurs more rapidly and residuals are less common than in acute viral hepatitis However subacute or massive hepatic necrosis may be fatal or may give rise to postnecrotic cirrhosis Occasionally death occurs as a result of an accompanying renal lesion despite satisfactory healing of the liver

The *diagnosis* is seldom difficult However errors are inevitable unless a specific inquiry about possible exposure to hepatotoxins is made in every case of hepatitis The sudden occurrence of oliguria and azotemia during an attack of acute hepatitis should always arouse suspicion of an intoxication even if there is no history of exposure particularly since poisoning may occur without the patient s knowledge

Treatment is very much like that described for acute viral hepatitis However greater consideration must be given to the status of the kidneys since hepatotoxins not infrequently produce acute renal tubular necrosis In such cases measures designed to reduce nitrogen retention and to attain a normal internal environment take precedence over

200 to 300 mg per day may be equally effective in some instances If the expected response is not obtained the dose of ACTH may be increased to 50 units As soon as the patient shows marked improvement usually in 2 or 3 days the dose of ACTH is reduced to 10 units and ultimately to 5 units To avoid the inconvenience of repeated infusions oral cortisone may be substituted for ACTH at any time during convalescence Similarly in less acutely ill patients cortisone may be used from the beginning starting with large doses and reducing them as rapidly as the clinical condition permits As indicated elsewhere sodium and potassium intake must be regulated and a watch must be kept for signs of toxicity There may be some advantage in substituting prednisolone for cortisone to minimize salt and water retention However experience with the former in the treatment of acute viral hepatitis is still rather limited

In the fulminant form of the disease with coma doses of cortisone up to 1 000 mg daily have been recommended However too few cases of this type have been treated in this manner to know whether massive therapy has any advantage over the usual dose levels employed

Treatment of Postnecrotic Cirrhosis and Its Complications The problems of therapy in this condition are very similar to those in Laennec s cirrhosis (p 1503)

Prevention

Since the patient with an IH viral infection passes the virus in his stools the usual sanitary measures employed in other enteric diseases must be initiated to prevent spread of the infection to others Unfortunately the duration of fecal infectivity is not known so that precise recommendations cannot be made regarding the length of the period during which precautionary measures must be followed However it is customary to carry them out until clinical recovery has been achieved

The blood is a source of infection in both types of viral hepatitis so that special care must be taken to avoid the transfer of virus to other patients through the agency of improperly sterilized blood contaminated instruments Preliminary washing followed by boiling for 10 min or preferably autoclaving for 15 min will ensure destruction of the virus The practice of using a single syringe with a change of needles for multiple injections in groups of patients is dangerous and is to be condemned

The selection of donors in blood banks is a difficult problem It is customary to eliminate individuals who have had viral hepatitis within a year However such persons appear to be a less danger ous source of infection than asymptomatic carriers with no history of previous disease Unfortunately there is no assured method of detecting such individuals but there is suggestive evidence that the incidence of abnormal liver function test results is unusually high in this group so that there is some hope that by screening all bloods by some simple technique such as the thymol turbidity test it may be possible to reduce the number of hazardous donors However some infected donors will escape detection and the number of presumably safe donors that must be rejected is so large that few blood banks have adopted this procedure Various methods of chemical treatment have been recommended to sterilize blood but none has proved satisfactory Since the possibility of infection cannot be eliminated with certainty the clinician would be well advised to limit the use of transfusions to conditions in which they are unequivocally indicated

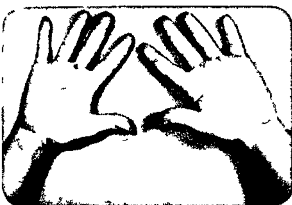
Commercially available plasma is even more dangerous than blood since large numbers of donors are used in making up a single pool If plasma must be used it should be obtained from as small a pool of donors as possible There is suggestive evidence that storage of plasma in the liquid state at room temperature for periods of 6 months or longer greatly reduces the risk of infection but other methods of sterilization that have been recommended are of little value

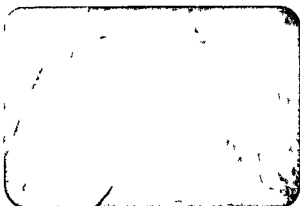
Individuals exposed to the IH type of viral hepatitis may be immunized passively by administering normal human gamma globulin at any time up to within 6 days of the expected onset of the disease The usual dose is 10 ml However recent evidence suggests that with very much smaller doses 0 01 ml per lb body weight it may be possible to achieve a more prolonged type of active passive immunity It is believed that under these conditions the gamma globulin suppresses the symptoms but does not prevent infection so that a natural acquired immunity develops It is doubtful that gamma globulin is of prophylactic value in SH viral infections although it has been reported that two injections of 10 ml each given at monthly intervals may be partially protective

Although gamma globulin is of particular value in the control of institutional and family epidemics there is no reason why it should not be used in any individual who has been exposed However the disease is so mild in healthy young children that it may be better to allow them to become infected and acquire a natural immunity

Toxic Hepatitis

The type of liver injury known as toxic hepatitis occurs following exposure to certain poisons and drugs or during the course of some systemic infections and metabolic disturbances True hepatotoxins such as carbon tetrachloride and phosphorus are tissue poisons that damage the liver by inacti





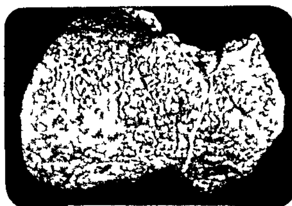








PLATE IV

(*A*) Hands of a 56 year old patient with portal cirrhosis held overhead showing liver palms with erythema of thenar and hypothenar eminences and finger pads (*B*) Numerous spider angiomata scattered over the right shoulder area of the same patient Note large solitary spider with central body and hairlike feet (*C*) Gross appearance of liver of same patient showing fine even nodularity or hob nailing and shrunken appearance (*D*) Same specimen in cut section showing even size of nodules and yellow color of increased fat content (*E*) Microscopic section (Masson stain) Note thickness of liver capsule increased amount of fibrous tissue in portal area and presence of fatty infiltration (*F*) Healed toxic cirrhosis (postnecrotic cirrhosis) following acute infectious hepatitis and chronic active hepatitis Note great thickness of connective tissue bands and isolation of parenchyma into small concentric hyperplastic nodule A mild inflammatory cellular infiltration persists and the small bile ducts show active hyperplasia Fat is inconspicuous

the less urgent needs of the liver This usually entails marked restriction or actual omission of protein provision of sufficient carbohydrate and fat calories to minimize protein catabolism and careful regulation of fluid and electrolyte balance

Hepatitis Due to Drug Hypersensitivity The features that characterize this type of hepatic damage and serve to distinguish it from that produced by true hepatotoxins include the following (1) the hepatitis occurs in only a small proportion of individuals exposed (2) neither the incidence nor the severity of the injury can be correlated with the amount of drug consumed (3) the lesion is not reproducible in animals (4) the onset of hepatitis bears no constant temporal relationship to the institution of drug therapy occurring with dramatic suddenness after the first dose in some individuals and only after prolonged administration or even following its withdrawal in others (5) the lesions are more variable than in toxipathic hepatitis and (6) signs of liver disease often are accompanied by other manifestations of hypersensitivity

Two generalizations are worth bearing in mind in interpreting the role of drugs in the pathogenesis of hepatitis (1) if a drug produces liver injury in man but fails to do so in other species it almost certainly is a sensitizing agent (2) if a drug gives rise to any other manifestations of hypersensitivity it can be predicted that sooner or later it will produce hepatitis in some individuals

Experimentally it has been shown that simple chemical compounds by combining with proteins may serve as antigens and induce hypersensitivity Similarly the striking clinical similarities between drug reactions and serum sickness suggest that the former are allergic in nature However drug reactions differ from the classical types of anaphylactic and tuberculin hypersensitivity in that (1) circulating antibodies and skin sensitivity can rarely be demonstrated (2) the interval between the first exposure to a drug and the appearance of a reaction is inconstant and (3) the manifestations of the reaction are unpredictable varying not only in different individuals but also with the particular drug involved It is especially difficult to explain why a single drug may produce fever and rash in one individual hepatitis in another or a depression of myelopoiesis in a third and why different drugs vary with respect to the frequency with which they induce one or another manifestation of hypersensitivity

The *morphologic changes* in the liver vary from case to case but in general fall into one of two patterns In the first which is more common there are irregularly distributed focal areas of parenchymal degeneration and necrosis and an intense portal inflammatory reaction with little or no fatty infiltration Occasionally the lesions are difficult to distinguish from those of acute viral hepatitis and rarely they are sufficiently extensive to produce the picture of subacute hepatic necrosis As a rule the lesions regress when the offending agent is withdrawn but occasionally the hypersensitivity reaction appears to trigger a progressive inflammatory process which may result in cirrhosis

The second type seen following reactions to chlorpromazine and the arsphenamines and less commonly after the sulfonamides neocinchophen and thiouracil is characterized by marked intralobular bile stasis and an intense predominantly mononuclear and eosinophilic inflammatory reaction in the portal triads In contrast the parenchymal cells show little or no change These features bear a striking resemblance to those of cholangiolitic hepatitis and extrahepatic biliary obstruction Occasionally the disease runs a long course despite the cessation of drug administration and rarely a type of biliary cirrhosis develops

The *clinical and laboratory features* of the more common type of drug hepatitis resemble those of acute viral hepatitis However the signs of liver disease are often preceded or accompanied by other manifestations of hypersensitivity such as fever rash arthralgia lymphadenopathy and signs of renal or hematopoietic injury Also there is a tendency for the serum alkaline phosphatase to be higher and the cephalin cholesterol and thymol turbidity reactions to be weaker than in viral hepatitis

In the type of hepatitis produced by drugs like chlorpromazine symptoms suggesting an extrahepatic biliary obstruction appear following a brief episode of fever and other constitutional symptoms The latter may or may not be associated with more distinctive signs of hypersensitivity Often the icterus is accompanied by dark urine and clay colored stools and pruritus may be a prominent feature The serum bilirubin and alkaline phosphatase levels tend to be as high as in obstructive jaundice while the cephalin cholesterol flocculation and thymol turbidity reactions are normal

Usually the hepatitis subsides within a few weeks following withdrawal of the offending drug However it may run a more chronic course occasionally terminating in a form of biliary cirrhosis (p 1506)

The *diagnosis* may be exceedingly difficult if there are no other manifestations of hypersensitivity A history of drug ingestion is helpful but obviously it does not exclude the possibility of an unrelated viral hepatitis or biliary obstruction Eosinophilia is an inconstant finding but when present favors a drug reaction Unfortunately even a liver biopsy may be inconclusive so that exploratory laparotomy may be indicated in cases with prolonged jaundice of doubtful etiology

In patients receiving a number of drugs it may be difficult to determine which is responsible for

the reaction Even a clinical trial following recovery may be misleading since multiple sensitivities may develop as a result of a reaction to a single drug Moreover it is unwise to carry out such tests since severe and even fatal reactions may ensue

The principles of *treatment* are the same as for toxipathic hepatitis In addition ACTH and cortisone may be useful adjuvants in severe illnesses Obviously at the first sign of a reaction the offending drug should be withdrawn However this may fail to abort the reaction Occasionally spontaneous or induced desensitization permits resumption of drug therapy following recovery However unless *the drug is urgently needed it is unwise to use it* again

Hepatitis Associated With Systemic Infections

Bacterial Infections Many systemic infections are accompanied by minor functional and structural changes in the liver that have little clinical significance Occasionally however severe bacterial infections give rise to sufficiently extensive hepatic lesions to produce jaundice and in rare instances may be responsible for progressive hepatocellular failure

Although the liver plays an important role in removing bacteria that gain access to the blood the parenchyma seldom becomes infected in the process More often the signs of hepatic damage which accompany systemic infections are due to circulating toxins or to the effects of such nonspecific factors as fever anemia hypoxia and malnutrition Some of the infectious agents involved are known to have in vitro hemolytic properties However except in the case of *Clostridium welchii* sepsis it is doubtful that hemolysis plays a significant role in the production of jaundice

Almost any severe bacterial infection may give rise to toxic hepatitis but the organisms implicated most frequently include pneumococci streptococci gonococci *Escherichia coli* and the *Salmonella* group While bacteremia is often present in such infections it does not appear to be essential for the development of toxic hepatitis as for example in pneumococcal pneumonia scarlet fever typhoid fever and food poisoning with *Salmonella typhimurium* and *Salmonella enteritidis*

The *pathologic changes* in the liver are nonspecific They may include focal areas of hepatocellular degeneration and necrosis signs of regeneration and an inflammatory reaction in the portal triads

The *clinical and laboratory features* resemble those in toxipathic hepatitis As a rule the signs of hepatic damage subside promptly as the underlying infection is brought under control In most cases the hepatitis does not appear to add materially to the severity of the illness However in rare in-stances severe hepatocellular failure may be contributory to a fatal outcome

Not all forms of jaundice accompanying severe infections can be attributed to toxic hepatitis In *E coli* bacteremia and in typhoid and paratyphoid fever it may be due to a complicating acute cholangitis while in *Cl welchii* sepsis it is usually the result of acute intravascular hemolysis and the destructive action of the invading organisms on the hepatic parenchyma Occasionally the jaundice that occurs in *Salmonella* and *Shigella* infections is due to a coincidental acute viral hepatitis Double infections of this type are not rare during concurrent epidemics of the two diseases Finally the possibility of a drug induced hepatitis must not be forgotten in evaluating the pathogenesis of any hepatitis that occurs during an infection.

Infectious Mononucleosis On the basis of histologic studies and tests of hepatic function it would appear that the liver almost always participates in the generalized inflammatory reaction of the reticuloendothelial system that characterizes infectious mononucleosis However overt clinical manifestations of hepatic involvement are relatively uncommon jaundice occurring in from 5 to 10 per cent of cases and hepatomegaly only slightly more frequently

The outstanding finding in the liver is an intense inflammatory reaction involving the sinusoids and portal triads The exudate is largely mononuclear consisting of atypical lymphocytes monocytes plasma cells and swollen proliferating Kupffer cells Occasionally the latter are arrayed in rosettes forming small granulomatous nodules in the sinusoids A few scattered parenchymal cells may exhibit early degenerative changes but hepatocellular necrosis is distinctly unusual despite the fact that the parenchymal cells often show evidence of active regeneration In jaundiced cases the canaliculi not infrequently contain bile thrombi Except for swelling and cellular infiltration, the portal triads are not altered

Abnormalities of "liver function" are demonstrable in most cases those depending on alterations in the serum protein pattern such as the cephalin cholesterol flocculation and thymol turbidity reactions predominating Since the latter can seldom be correlated with evidence of hepatocellular injury histologically and since they often persist long after clinical recovery it is highly probable that they are in part at least due to nonspecific changes in serum protein related to the underlying infection Characteristically the serum albumin level falls while the gamma globulin concentration rises Occasionally there is a less pronounced increase in alpha 1 and beta globulin Strongly positive cephalin cholesterol flocculation reactions and increased levels of thymol turbidity are seen in at least 80

other forms of tuberculosis however signs of liver disease are unusual except for slight hepatomegaly and nonspecific minor alterations in function which may be unrelated to the presence of hepatic granulomas

Three rare forms of hepatic tuberculosis are characterized by marked enlargement and tenderness of the liver chills and fever jaundice and a rapid downhill course They are (1) pylephlebogenous tuberculosis in which there is massive dissemination of tubercle bacilli to the liver by way of the portal vein from an intraabdominal focus (2) hepatic tuberculomas which are large caseating masses or abscesses of tuberculous origin and (3) tuberculous cholangitis or tubular tuberculosis of the liver a condition which arises as a result of rupture of a caseating tuberculoma or abscess into the biliary tract and subsequent spread of the infection along its course

Brucellosis Granulomas can be demonstrated in the liver in a high proportion of patients with active *Brucella abortus* infections they are relatively uncommon in *Brucella suis* and *Brucella melitensis* infections

The lesions seldom give rise to clinical manifestations although hepatomegaly is common Several instances of jaundice have been reported but they are rare Hepatic function is little impaired and may be normal even in the presence of granulomas

Occasionally cirrhosis is a late complication of brucellosis It is still not certain whether this is a sequel to healing of granulomas or the consequence of associated malnutrition

Cirrhosis

Any diffuse fibrosis that destroys the normal lobular architecture of the liver may be properly classified as a form of cirrhosis Characteristically the parenchymal cells lying between the connective tissue septums are arranged in islands that differ from normal lobules not only in size and shape but also in their lack of normally oriented central veins and portal triads They may represent segments of lobules isolated by encircling fibrous bands or nodules of regenerating parenchyma and may vary in size from less than a millimeter to several centimeters in diameter Other features seen in many but not all cases of cirrhosis include degeneration atrophy and necrosis of parenchymal cells an inflammatory reaction usually most marked in the periportal areas proliferation of the small perilobular bile ducts and alterations in the intrahepatic vasculature characterized by compression distortion and reduction in the size of either the portal or hepatic venous bed and the occurrence of abnormal shunts between the major vascular components of the lobules In addition, there may be a number of changes related to the specific effects of certain etiologic factors The deposition of iron containing pigment in hemochromatosis may be cited as an example

Although there are well-defined differences in the pathogenesis of the several known types of cirrhosis the basic fibrotic process in all appears to be the consequence of hepatocellular necrosis or atrophy resulting in collapse and condensation of the normal supporting reticulum followed by deposition of collagen It is doubtful that the apparent proliferation of connective tissue from periportal and pericentral foci is the primary cause of parenchymal replacement although it may contribute to the process by compressing adjacent hepatic cells or by reducing their blood supply

As the cirrhotic process advances signs of hepatocellular failure and portal hypertension appear owing to progressive degeneration and obliteration of the parenchyma and to obstruction to the outflow of portal blood However cirrhosis is not always progressive Indeed, the disease may remain asymptomatic or may regress once overt manifestations have appeared Although experimental evidence suggests that even fibrosis may diminish under certain conditions the improvement that occurs in man appears to be due to the recovery of injured liver cells the replacement of lost cells by active regeneration and the resolution of inflammatory exudates

Occasionally the etiology of the cirrhotic process may be inferred from the morphologic changes in the liver but more often the differentiation among the several known types of cirrhosis depends in part at least on collateral historical and clinical evidence This is not surprising considering the limited number of ways in which the liver can react to diverse types of injury

The forms of cirrhosis that are recognized clinically include the following (1) Laennec s (2) postnecrotic (3) biliary (4) cardiac (5) hemochromatosis (6) hepatolenticular degeneration (Wilson s disease) (7) cirrhosis due to schistosomiasis and (8) rarer types

Laennec s Cirrhosis

Definition Laennec s cirrhosis by far the most common type encountered is characterized by a fine diffuse fibrosis of the liver often accompanied by fatty infiltration and degeneration of the parenchyma Malnutrition and chronic alcoholism are the major factors involved in its pathogenesis but in some instances the etiology is obscure Occasionally the hepatitis virus and certain poisons give rise to lesions which in their late stages closely resemble those of Laennec s cirrhosis However because of the manner in which they develop such lesions are usually classified as forms of postnecrotic cirrhosis

per cent of cases Bromsulphalein retention increases in serum alkaline phosphatase and urine urobilinogen and decreases in prothrombin and serum cholesterol esters are less common findings Hyperbilirubinemia and bilirubinuria occur in from 10 to 30 per cent of cases

In general the histologic changes and alterations in hepatic function parallel the severity of the underlying infection What role the former play in producing clinical manifestations is difficult to assess However it is doubtful that the minor changes in the liver that occur in most anicteric cases contribute significantly to the symptomatology or clinical course of the disease When the hepatic lesions are more extensive and particularly when jaundice occurs the symptoms may resemble those of acute viral hepatitis suggesting that they are of hepatic origin

The jaundice that occurs in infectious mononucleosis tends to be mild and usually clears up within a few weeks Its appearance may precede or coincide with the onset of lymphadenopathy Occasionally the lymph nodes fail to enlarge in which case the etiology of the fever and jaundice may be more difficult to identify Often the jaundice is accompanied by slight tenderness and enlargement of the liver and by splenomegaly The other clinical manifestations of infectious mononucleosis are described elsewhere (p 1151)

The biochemical changes suggesting hepatic involvement usually return to normal by the end of the second month but in occasional instances they persist for many months However there is no convincing evidence that infectious mononucleosis gives rise to cirrhosis or to any other form of chronic hepatic disease

In the presence of jaundice it may be difficult to differentiate infectious mononucleosis from acute viral hepatitis The occurrence of sore throat significant lymphadenopathy or chills favors the former Atypical lymphocytes may appear in the blood in both diseases but seldom exceed 10 per cent of the total leukocyte count in acute viral hepatitis In the last analysis the diagnosis must be established serologically (p 1153)

The hepatic lesions of infectious mononucleosis require no special treatment There is no convincing evidence to indicate that dietary measures shorten the course of the disease or have any effect on the symptoms

Leptospirosis See p 1014

Granulomatous Hepatitis

The liver often participates in generalized granulomatous reactions of such varied etiology as sarcoidosis tuberculosis brucellosis certain mycoses and berylliosis The lesions which consist of discrete collections of epithelioid and giant cells apparently derived from the reticuloendothelium to displace adjacent hepatic cells as they exp However they usually remain quite small so the loss of parenchyma is minimal even wher lesions are numerous Rarely they coalesce to large lesions in which case they may produce and symptoms of liver disease

As a rule it is difficult to distinguish betw the hepatic granulomas of different diseases morphologic basis alone Central necrosis is common in tuberculosis brucellosis and my infection than in sarcoidosis and berylliosis b is an inconstant finding and caseation whic such a common feature in tuberculous lesions where in the body is rare in the liver Occas ally by means of special stains or cultural meth it is possible to demonstrate the underlying etiol agent

Sarcoidosis In approximately 70 per cen patients with sarcoidosis it is possible to den strate the presence of hepatic granulomas by m of needle biopsy Since this approaches the i dence found at autopsy it may be inferred usually the lesions are numerous and unifor distributed Nevertheless they seldom give ris symptoms although mild degrees of hepatome and minor alterations of function are common high serum alkaline phosphatase level seen in disease appears to be more closely related to presence of hepatic granulomas than to the currence of lesions in bone Rarely the granulo tous reaction and the fibrosis that follows are extensive that overt signs of liver disease app These signs may include marked hepatomeg jaundice ascites splenomegaly and bleed esophageal varices and they may be mistaken evidence of other types of cirrhosis especially there are no extrahepatic manifestations of coidosis As a rule the diagnosis depends on l biopsy although it may be suspected when th are other signs of the disease

Tuberculosis Needle biopsy studies indicate t hepatic granulomas can be demonstrated in m patients with acute miliary tuberculosis and in proximately half of those with other forms of disease Presumably the lesions are indicative o hematogenous spread of the infection but si acid fast organisms can seldom be demonstrat the question arises whether the granulomas m not represent a nonspecific response to the infecti In addition to the granulomas fatty infiltrati portal fibrosis and less commonly Laennec's c rhosis may be found These appear to be relat to the malnutrition which may accompany this d ease

Occasionally the number of hepatic granulom in acute miliary tuberculosis is so great that signi cant hepatomegaly and jaundice develop In mo

develop cirrhosis than undernourished invalids whose diets are likely to be deficient in both protein and calories

It should be noted that while chronic alcoholism may be an important factor in the pathogenesis of cirrhosis only a small proportion of chronic users of alcohol actually develop cirrhosis No doubt differences in dietary habits play a role but marked differences in individual susceptibility appear to be an equally important factor This has been confirmed in animal experiments

Pathology In the incipient stage of the disease the liver is enlarged and pale owing to the presence of large fat globules in the parenchymal cells As these become more numerous stellate shaped areas of fibrosis appear in the portal areas and to a lesser extent around the central veins Later thin connective tissue septums join the portal triads and traverse the lobules breaking them up into islands of cells which tend to proliferate forming small nodules or pseudolobules As the disease progresses the fibrous bands become thicker and more numerous are infiltrated by mononuclear cells and incorporate an increasing number of blood vessels and regenerating perilobular bile ducts At the same time foci of degeneration and necrosis infiltrated with mononuclear and polymorphonuclear cells appear in the parenchyma while the amount of fatty infiltration tends to decline Often the cytoplasm of the hepatic cells contains highly characteristic eosinophilic droplets and club shaped masses of hyalinelike material known as *Mallory bodies* These are especially common when chronic alcoholism is an etiologic factor and may be very numerous when the disease is severe In jaundiced patients the canaliculi may contain plugs of inspissated bile and occasionally there is bile staining of the parenchymal and Kupffer cells

Late in the disease the liver is firm and finely nodular or granular but occasionally it is coarsely nodular with broad intervening connective tissue septums very much as in postnecrotic cirrhosis Whether this represents a morphologic variant of Laennec s cirrhosis dependent on a more acute patchy type of necrosis with more active regeneration than in the usual case or whether it is the sequela of an unrecognized intercurrent infection with the hepatitis virus is still uncertain The size of the liver is variable being small in some cases and large in others

As previously indicated the fibrosis in Laennec s cirrhosis appears to be the consequence of hepatocellular necrosis and collapse of normal supporting reticulum Whether fatty infiltration plays an important role in this process is still uncertain, particularly since fatty livers do not necessarily become fibrotic In animal experiments it has been shown that large fat globules in adjacent cells tend to coalesce forming large cysts and that as the fat is reabsorbed the reticulum fibers derived from the original cells collapse to form a network of fine septums which ultimately undergo collagenization. However it is doubtful that this is the only way in which fibrosis can develop

In the florid form of Laennec s cirrhosis which occurs exclusively in alcoholic addicts the predominant findings are extensive and there is severe hepatocellular degeneration and necrosis with numerous Mallory bodies and infiltrating polymorphonuclear cells Fatty infiltration and fibrosis vary in extent and may be negligible

Clinical Features Usually the onset is insidious with nonspecific complaints including anorexia weakness and unusual fatigability that relate both to early hepatic dysfunction and the accompanying underlying malnutrition and chronic alcoholism Although weight loss is common late in the disease it may be absent in its early phases This relates to the fact that while the alcoholic addict is malnourished in the sense that the quality of his diet is poor he frequently obtains a sufficient number of calories in the form of alcohol to maintain or even gain weight Similarly the natives of tropical areas who develop nutritional cirrhosis often show no evidence of wasting since their caloric intake in the form of carbohydrate tends to be high despite a deficiency of protein

As the disease advances signs of frank hepatocellular failure and portal hypertension appear The former include jaundice ascites edema pleural effusion, alterations in serum electrolytes spider nevi palmar erythema gynecomastia testicular atrophy impotence loss of axillary and pubic hair and a bleeding tendency (pp 146 150) the latter splenomegaly esophageal varices with or without massive bleeding and a visible venous collateral circulation over the abdomen (p 149) Usually the symptoms of hepatocellular failure dominate the clinical picture but not infrequently the signs of portal hypertension can be demonstrated even before symptoms appear and occasionally massive bleeding from esophageal varices is the initial manifestation

Low grade fever nausea vomiting diarrhea and abdominal pain are common complaints in the stage of advanced hepatic failure As indicated previously the pathogenesis of these symptoms is uncertain Usually the pain is mild and aching in character but occasionally and especially in the florid form of the disease it may be severe and cramping and may be mistaken for biliary colic or a sign of ruptured peptic ulcer Hepatomegaly is an inconstant but fairly frequent finding When palpable the liver usually is very firm occasionally it is

Laennec's cirrhosis is known also as *alcoholic fatty portal* or *atrophic* cirrhosis These terms would appear to be inappropriate since (1) alcohol is not always an etiologic factor (2) fatty infiltration is not demonstrable in all cases (3) the fibrous septums radiate not only from the portal triads but also from the central veins and (4) the liver may be either large or small depending on the relative degrees of fatty infiltration fibrosis and hepatocellular necrosis and regeneration

Etiology Laennec's cirrhosis is thought to be the consequence of a specific type of malnutrition usually related to chronic alcoholism and/or faulty dietary habits In this country and in many parts of Europe chronic alcoholism is a major etiologic factor in approximately 75 per cent of cases but in England and in other parts of the world it plays a relatively unimportant role A faulty diet almost certainly accounts for the prevalence of the disease among nonalcoholics in certain tropical and subtropical areas but does not appear to be a significant factor in the pathogenesis of cirrhosis among nonalcoholics in the Temperate Zone On the basis of indirect evidence it has been suggested that viral hepatitis may be of etiologic importance in such cases To be sure the hepatitis virus is capable of producing a finely nodular cirrhosis but the resulting lesion differs from that in the usual form of Laennec's cirrhosis not only in its mode of development but also in many of its histologic features and hence should be classified as postnecrotic along with other forms of posthepatitic cirrhosis

Occasionally Laennec's cirrhosis is a complication of other diseases In a few instances the lesion appears to be the consequence of malnutrition due either to an absorptive defect as in pancreatic insufficiency or to a poor dietary intake as in ulcerative colitis chronic malaria and chronic dysentery but in other conditions such as diabetes mellitus galactosemia and thyrotoxicosis the pathogenesis of the cirrhosis is obscure

It is generally agreed that alcohol is not a hepatotoxin and that its effects on the liver probably are secondary to an associated nutritional disturbance However the nature of the deficiency and the precise mechanism responsible for the development of cirrhosis are still uncertain According to one widely held theory excessive drinking merely reduces food intake and thus leads to a deficiency of lipotropic substances including choline its precursor methionine vitamin B_1 folic acid and possibly some of the other amino acids like threonine lysine and tryptophan that affect the lipid content of the liver As a result the liver becomes fatty and ultimately undergoes fibrosis It is believed that the accumulation of fat under these conditions is due to a reduced rate of fatty acid oxidation in the liver but it is not known whether the fibrosis is the direct consequence of fatty infiltration or an independent sequela of the lipotropic deficiency *In support of* the lipotrope theory it has been shown that (1) diets rich in protein and hence high in lipotropic activity are effective in the treatment of Laennec's cirrhosis (2) it is possible to produce a similar lesion in animals by reducing the intake of protein and other lipotropic substances and (3) the diet in tropical and subtropical areas where Laennec's cirrhosis is common is low in protein content However it has been found that in animals on low protein diets and in children with kwashiorkor a form of malignant malnutrition seen in the tropics supplements of protein are far more effective in reversing the associated hepatic lesions than equivalent amounts of choline or methionine suggesting that the injurious effects of low protein diets on the liver are due to more than a simple deficiency in lipotropic activity Moreover since the hepatic lesions of uncomplicated protein deficiency show few of the characteristic degenerative and inflammatory changes seen in Laennec's cirrhosis the question arises whether nondietary factors may not be involved in their pathogenesis In particular the role of infection merits further investigation since intercurrent bacterial infections so often appear to accelerate the progress of the lesions in Laennec's cirrhosis Moreover the unusual incidence of carriers of the hepatitis virus among alcoholic addicts with cirrhosis suggests the possibility that activation of the virus may be a factor in the evolution of the lesion in some instances

A number of clinical observations cast doubt on the concept that the effects of chronic alcoholism on the liver are due solely to a reduction in food consumption In particular it may be pointed out that alcoholic addicts occasionally develop Laennec's cirrhosis despite an apparently adequate dietary intake and that simple undernutrition such as occurs in many chronic illnesses seldom gives rise to cirrhosis Recent animal experiments have shed some light on this problem They have shown that while the ingestion of alcohol leads to a decrease in food consumption apparently in response to the homeostatic mechanism controlling the caloric intake it also raises the requirement for lipotropic substances first by increasing the total caloric intake and second by some other as yet unidentified mechanism not dependent on the calorigenic activity of alcohol These observations may explain why apparently adequate diets occasionally fail to protect against the development of cirrhosis in individuals who consume a large number of alcohol calories and why the natives of tropical and subtropical areas whose diets are low in protein but high in carbohydrate calories are more likely to

that more effective methods of combating infection and controlling hemorrhage and more stringent control over the patient s drinking habits and phys ical activity have contributed to the results It should be noted in this connection that intercurrent infection and hemorrhage still account for almost half the deaths that occur which emphasizes the need for meticulous care and close supervision of the cirrhotic patient

Treatment A nutritious diet strict prohibition of alcohol judicious regulation of salt and water bal ance prompt control of hemorrhage and replace ment of lost blood a prompt and vigorous attack on all intercurrent infections and provision for ade quate rest are the mainstays of treatment in Laen nec s cirrhosis

A palatable *diet* containing from 80 to 120 Gm protein and 2500 to 3000 cal depending on the patient s size and degree of malnutrition appears to be adequate for the needs of the liver and the re plenishment of depleted tissue stores There is no convincing evidence that a larger intake of protein is more effective as far as the recovery of the liver is concerned but it may restore the wasted tissues more rapidly However it usually is difficult to get sick patients to consume such large diets and there is the potential hazard of precipitating hepatic coma in those with extensive portacaval shunting There is no need to restrict fat so that the patient s per sonal preferences and tolerance may be used as a guide in adjusting the ratio of fat to carbohydrate calories

Vitamin supplements are indicated in patients with overt signs of deficiency and in those who will not or cannot eat but they are an unnecessary ex pense to patients who are consuming a well bal anced diet Similarly *choline* and *methionine* sup- plements may be helpful in individuals with fatty livers who are poor eaters but they are of no value if the protein intake is adequate Moreover methio- nine may be toxic in some individuals (p 152) *Intravenous liver extract* and *vitamin* B_1 are al leged to stimulate the appetite but the evidence for this is not convincing *ACTH* and *cortisone* are more effective in stimulating the appetite and create a sense of well being but the frequency of unde sirable side effects such as increased fluid reten tion hemorrhage from esophageal varices and un recognized peptic ulcer and portal vein thrombosis contraindicates their use except under special cir cumstances *Testosterone propionate* has been rec ommended on the grounds that it facilitates protein storage and increases the patient s strength How ever the minimal benefits to be derived do not appear to justify the cost and inconvenience of such therapy

Salt restriction is the simplest and one of the most effective means of managing fluid retention and should be the first employed when ascites edema and hydrothorax appear (p 148) Often limitation of the sodium intake to 500 mg (22 mEq) a day will suffice but it may be necessary to reduce the intake to 200 mg (10 mEq) to promote a diuresis Unfortunately restricting salt makes it difficult to prepare diets rich in protein. However this can be achieved by the use of salt poor deriva tives of milk protein like Lanolac and salt free bread If salt restriction is ineffective in relieving edema and ascites *mercurial diuretics* and *am monium chloride* may be used provided the po- tential hazards of salt depletion (p 149) and am monia intoxication (p 152) are kept in mind Intravenous infusions of *concentrated human al bumin* may be helpful in producing a diuresis when other measures have failed and occasionally for reasons that are not clear they appear to improve the general clinical status of severely ill patients Unfortunately they may produce bleeding from esophageal varices or may precipitate pulmonary edema if given too rapidly so that they must be used with caution and only when other therapeutic measures have been ineffective *Paracentesis* and *thoracentesis* are indicated whenever the amount of fluid accumulated is sufficiently great to produce symptoms Their number should be kept to a mini mum since they waste protein and subject the pa tient to the hazards of the salt depletion syndrome Application of a tight abdominal binder and restric tion of water for a period of 24 hr following para centesis will do much to prevent the latter If this fails a slow infusion of albumin to maintain the blood volume may be more effective Obviously sodium administration is indicated once the salt depletion syndrome has appeared

The occurrence of massive bleeding from esoph ageal varices calls for immediate *balloon tamponade* of the esophagus and *transfusion* of whole blood In transfusing blood an attempt should be made to replace the estimated loss and to maintain the hematocrit at a normal level The triple lumen double balloon tube described by Sengstaken and Blakemore appears to be the most effective type of tampon available The inflated lower balloon anchors the tube at the cardia, while the upper one compresses the bleeding varices Two of the lumens are used for inflating the balloons while the third is used for aspirating gastric contents and for feeding Frequent checks on the pressures in both balloons are essential since many failures are at tributable to their improper inflation and place ment The tube is deflated 72 hr after blood can no longer be aspirated from the stomach, but is left in place for another 24 hr to detect any recurrence of bleeding It may be necessary to reinflate the balloons several times before a firm clot is formed There is the danger of course that tamponade for

slightly tender The nodules on its surface can rarely be felt

Impending and overt hepatic coma usually are *signs of terminal hepatocellular failure* However they may be indicative of portacaval shunting of nitrogenous substances from the intestine as a consequence of massive hemorrhage or the ingestion of excessive amounts of protein (p 152) and they may be reversible

In the florid form of the disease the onset tends *to be more acute and the* progression of symptoms *more rapid and less responsive to treatment* Often nausea vomiting abdominal pain high fever and marked leukocytosis are prominent features

Usually hepatic decompensation is the consequence of progressive hepatocellular failure resulting from prolonged malnutrition and overindulgence in alcohol However it may be precipitated acutely by *massive gastrointestinal* bleeding intercurrent *infection* surgical trauma or the development of a complicating hepatoma

The principal complications of Laennec s cirrhosis include bleeding from esophageal varices hepatoma portal vein thrombosis and intercurrent infection Bacteremia apparently arising in the tributaries of the portal vein is an occasional terminal event Peptic ulcer and acute pancreatitis are *common complications* but appear to be more *closely* related to the accompanying chronic alcoholism than to the cirrhosis

Laboratory Features The results of *liver function tests* point to hepatocellular damage Bromsulphalein retention is an almost invariable finding even when other tests are negative The serum albumin level falls progressively as the disease advances while the serum globulin and especially the *gamma fraction* tends to rise The direct and total serum bilirubin concentrations may be normal but often are increased to a variable degree The cephalin cholesterol flocculation test usually is positive but thymol turbidity often remains normal The serum alkaline phosphatase concentration tends to increase slightly but occasionally it rises to the levels seen in obstructive jaundice In most cases there is no change in the total serum cholesterol but often the unesterified fraction is increased especially when jaundice is present A subnormal cholesterol concentration usually signifies advanced hepatocellular failure and is a bad prognostic sign All these changes tend to revert to normal under treatment although Bromsulphalein retention usually persists

Moderate *anemia* is a common finding Usually it is normocytic or slightly macrocytic in character and often it is accompanied by a hyperactive normoblastic bone marrow mild reticulocytosis and a decrease in the red cell survival time features suggesting a hemolytic basis possibly related to overactivity of the spleen although other factors cannot be excluded As might be expected *treatment with iron liver extract and vitamin B_1 is seldom* effective A few instances of frank hemolytic anemia with a positive Coombs test result have been reported These have been attributed to hypersplenism" Occasionally the anemia is microcytic and hypochromic as a result of chronic blood loss from esophageal varices or hemorrhoids Rarely the anemia is megaloblastic and *responds to vitamin* B_1 or citrovorum factor suggesting a nutritional basis

Slight *leukopenia* and *thrombocytopenia* are common and probably represent manifestations of "hypersplenism As previously mentioned *leukocytosis* is the rule in florid cirrhosis the count often ranging between 20 000 and 50 000 per cubic millimeter In other cases lesser degrees of leukocytosis may occur when there is active hepatocellular necrosis and degeneration

Diagnosis With a history of chronic alcoholism or malnutrition a firm liver and signs of hepatocellular failure and portal hypertension the diagnosis of Laennec s cirrhosis presents no problem However in the absence of any one or several of these features the differentiation from other diseases may be difficult The particular disorders to be considered in any given case will depend on the presenting manifestations they include such diverse conditions as other forms of cirrhosis hepatitis intrahepatic malignancy portal and hepatic vein obstruction congestive heart failure constrictive pericarditis various infiltrative and granulomatous diseases that involve the liver and spleen and bleeding peptic ulcer Usually a thorough clinical investigation including tests of liver function will serve to distinguish among these disorders but in doubtful cases a biopsy of the liver may be required

Prognosis There is no doubt that the modern all out therapeutic attack on Laennec s cirrhosis is effective in restoring many patients to good health provided vigorous treatment is begun at an early stage of the disease This is reflected in the increased life expectancy reported by several investigators However the mortality rate is still distressingly high in patients with advanced hepatocellular failure or bleeding esophageal varices Thus of patients with ascites approximately 35 per cent are dead in 1 year 50 per cent in 2 years and 70 per cent in 5 years Even more alarming statistics may be cited for the group with massive bleeding but there is some hope that *recently* developed surgical techniques for controlling portal hypertension may reduce these figures

The improvement in the outlook for the cirrhotic patient usually is credited to the introduction of modern dietary therapy However while this represents an important advance there is little doubt

acteristic picture of large nodules separated by broad bands of stromal collapse and fibrosis The size of the nodules and the breadth of the connective tissue septums vary depending on the distribution and extent of the original necrosis In typical cases broad zones of necrosis traverse the parenchyma subdividing it into large lobular aggregates which tend to proliferate thereby increasing the size and distorting the architecture of their constituent lobules Occasionally the necrosis is so extensive that an entire lobe usually the left is destroyed leaving nothing but stroma A finely nodular or granular cirrhosis may be produced if the zones of necrosis and collapse are diffusely distributed in a fine pattern This type may be difficult to distinguish from Laennec's cirrhosis unless the process is active and some of the characteristic histologic features of the underlying acute disease are still evident

Postnecrotic cirrhosis is known by a variety of other names including *postnecrotic scarring toxic cirrhosis posthepatitic cirrhosis coarsely nodular cirrhosis healed yellow atrophy* and *Marchand's multiple nodular hyperplasia*

Etiology Most instances of postnecrotic cirrhosis represent the sequelae of subacute hepatic necrosis due to the hepatitis virus (p 1487) In some the manifestations of cirrhosis follow so closely on the heels of a typical attack of acute viral hepatitis that there can be little doubt about the etiology but in others the onset is insidious so that the viral origin of the lesion must be inferred from either the character of the histologic changes in the liver or a history suggestive of infection in the past Less commonly postnecrotic cirrhosis is the consequence of subacute hepatic necrosis due to poisoning with carbon tetrachloride chloroform the chlorinated naphthalenes and diphenyls tetrachlorethane TNT or mushrooms (*A phalloides*) or to the administration of drugs like cinchophen

Late in the disease there may be none of the earmarks of the acute necrosis responsible for the fibrosis so that the viral or toxic origin of the lesion may be difficult to establish especially if the nodules are of the small variety Many instances of cirrhosis seen among nonalcoholics fall into this group Occasionally a coarsely nodular cirrhosis resembling the postnecrotic variety is seen in the de Toni Fanconi syndrome a congenital renal tubular defect associated with hypophosphatemia rickets glycosuria and aminoaciduria and in hyperthyroidism The pathogenesis of the cirrhosis in these cases is obscure

Animals fed a diet low in cystine methionine tocopherol and an agent found in casein develop a type of subacute or massive hepatic necrosis which on healing gives rise to necrotic cirrhosis Accordingly it has been proposed that the hepatitis virus poisons and drugs may induce a deficiency of essential sulfhydryl groups in the liver by interfering with the intrahepatic circulation by diverting sulfhydryl groups to other purposes or by increasing the demands for sulfhydryl groups and thus produce subacute hepatic necrosis and postnecrotic cirrhosis However there is no convincing evidence that any of these mechanisms is involved in the pathogenesis of postnecrotic cirrhosis in man.

Pathology The evolution of the lesion in the viral type of postnecrotic cirrhosis has been described elsewhere (p 1487) Except for the occurrence of fatty infiltration early in the course of the disease the zonal distribution of the necrosis and the character of the inflammatory reaction which tends to be less extensive but more polymorphonuclear in type the toxic form of postnecrotic cirrhosis develops in the same manner

The features that distinguish the posthepatitic type from Laennec's cirrhosis include the following (1) the nodules usually are larger vary more in size and shape and often contain several intact but abnormally oriented central veins and portal triads (2) the septums tend to be broader show a more intensive mononuclear inflammatory reaction and contain many more blood vessels regenerating bile ducts and collapsed and thickened reticulum fibers but fewer collagen fibers (3) the parenchyma shows a more active type of regeneration with the appearance of bizarrely shaped multinucleated cells and often exhibits eosinophilic Councilman like hyaline bodies (p 1487) scattered foci of necrosis and degeneration and a mononuclear exudate (4) often the veins show an inflammatory reaction in their walls and (5) fatty infiltration and Mallory bodies (p 1501) are rare

Clinical Features Often the overt manifestations of cirrhosis appear insidiously (1) during convalescence from an otherwise uncomplicated and sometimes very mild attack of acute viral or toxic hepatitis (2) after one or more relapses following an attack of acute hepatitis (3) following a vague anicteric illness presumably due to the hepatitis virus or (4) in an individual in apparent good health who may or may not give a history of previous hepatitis Occasionally the onset is acute and severe with signs of subacute hepatic necrosis (p 1490) following which progression to the stage of fibrosis may be remarkably rapid

The clinical features are very much like those of Laennec's cirrhosis (p 1501) except that (1) jaundice appears at an earlier phase and is more likely to be persistent or to recur at intervals (2) abdominal pain and gastrointestinal symptoms are more frequent and tend to be more severe (3) purpura epistaxis and other hemorrhagic phenomena are more common, (4) the liver tends to be smaller and is more often nodular on palpation (5) once

more than 5 or 6 days may produce esophageal ulceration However this risk must be accepted since uncontrolled hemorrhage is likely to be fatal Another hazard of tamponade to be guarded against is asphyxia due to displacement of the balloon up into the pharynx Usually this can be avoided by fixing the tube at the external nares by means of tape rather than by applying traction with a suspended weight and by using restraints on the patient s hands if he is uncooperative and shows any tendency to tug at the tube If the tube slips and respiratory distress ensues the tube should be cut with a pair of scissors and pulled out at once Attempts to deflate both balloons in the usual way may be disastrous Since the regurgitation of gastric juice may be a factor in the pathogenesis of variceal ulceration and in the prevention of firm clot formation suppression and neutralization of gastric secretion should be attempted by administering Banthine and antacids If the prothrombin time is prolonged large doses of vitamin K are indicated

If hemorrhage from esophageal varices cannot be controlled by conservative measures emergency surgical intervention may become necessary The procedures used include ligation of the hepatic and splenic arteries resection of the cardia and lower esophagus and transthoracic transesophageal suture of the bleeding varices Of these the last has proved to be most effective and least hazardous However the mortality following any of these procedures is high so that none should be undertaken unless it is certain that tamponade and transfusion are ineffective and that the degree of hemorrhage is a threat to life

Once a patient has had a massive hemorrhage from esophageal varices the risk of recurrence is great even after ligation of the vessels and strict adherence to a good medical regime and with each subsequent hemorrhage the chances of survival diminish For that reason there is a growing tendency to advise a surgical attack on either the underlying portal hypertension or the site of varix formation as soon after the first hemorrhage as the patient s condition permits The most impressive results have been obtained with portacaval shunts Recurrences of massive hemorrhage have been infrequent and there is suggestive evidence that longevity has been increased However while it has been shown that 70 per cent of the patients operated upon are alive after 2 years as against only 20 per cent for randomly collected untreated cases little attention has been paid to the fact that the patients selected for surgery have in general been the ones in the best condition and hence the ones most likely to survive multiple hemorrhages if left untreated Nevertheless it cannot be denied that if hemorrhage is prevented the chances of survival for the cirrhotic patient must be improved Unfortunately the postoperative mortality rate following portacaval shunt is still approximately 20 per cent so that the decision whether to operate and when requires fine judgment

Ligation of the hepatic and splenic arteries with splenectomy in the hope of reducing portal pressure is less effective than portacaval shunt and carries an even higher mortality rate *Resection of the cardia and lower esophagus* in an attempt to remove the site of varix formation is used but cannot be recommended since recurrences of varices and hemorrhage are common Recently there has been a renewal of interest in the *injection of esophageal varices* with sclerosing solutions While this is not the treatment of choice since varices are likely to recur it may be useful in patients whose physical condition contraindicates a surgical procedure or in individuals in whom thrombosis of the portal and splenic veins makes portacaval shunt impossible

A period of *bed rest* is strongly recommended for the sick cirrhotic patient Not infrequently it is followed by striking improvement in individuals who have done poorly on an otherwise exemplary regime Similarly in ambulatory patients physical activity should be regulated in an attempt to avoid undue fatigue and exhaustion The basis for the efficacy of rest is not known it may be related to the increase in hepatic blood flow and decrease in over all metabolic activity that accompany inactivity and recumbency

The principles of treatment in hepatic coma are based on current concepts of its pathogenesis (p 152) They include (1) restriction or omission of protein and provision for maintenance of caloric needs in the form of carbohydrate and fat in the comatose patients 2 to 2 5 liters of intravenously administered 15 per cent glucose will suffice (2) correction of any deficits in water blood or electrolytes (3) administration of glutamate either intravenously as the sodium salt in doses of 25 to 50 Gm daily or as the free acid by mouth or by tube at the rate of 2 Gm hourly and (4) broad spectrum antibiotics either orally or by tube Aureomycin Terramycin and neomycin in full therapeutic doses appear to be the most effective If these measures fail it is worth trying large doses of ACTH and cortisone since occasional responses are seen

Postnecrotic Cirrhosis

Definition In contrast to Laennec s cirrhosis which is characterized by the gradual disintegration of cells in small symmetrical foci giving rise to a fine diffuse fibrosis with small nodules postnecrotic cirrhosis is the result of a more acute type of necrosis involving larger areas of parenchyma in a more irregular pattern which produces a char

biliary cirrhosis was called *xanthomatous biliary cirrhosis* in the belief that the xanthomatosis was a manifestation of a primary disturbance in lipid metabolism and that the hepatic lesion was secondary to xanthomatous obstruction of the biliary tract However it is now known that the hypercholesteremia and xanthomatosis in both extra and intrahepatic biliary cirrhosis are manifestations of the underlying liver disease and bear no relationship to familial hypercholesteremia and xanthomatosis and that xanthomatous deposits in the biliary tract play no role in the pathogenesis of cirrhosis It should be emphasized that not all cases of biliary cirrhosis develop xanthomatosis the occurrence of such lesions depending on the magnitude and duration of the serum lipid elevation In general xanthomas occur more frequently in the primary intrahepatic type than in any of the other forms of biliary cirrhosis The longer duration of the disease in the former and the greater delay in the appearance of hepatocellular failure which tends to lower the serum lipids probably account for this difference

Other synonyms sometimes applied to the primary type of intrahepatic biliary cirrhosis include *Hanot s hypertrophic pericholangiolitic cholangiolitic* and *nonobstructive cholangitic biliary cirrhosis*

Pathology Following occlusion of the extrahepatic bile ducts the liver shows a number of characteristic changes which include (1) signs of bile stasis as evidenced by the presence of bile thrombi in the central canaliculi and bile staining of scattered parenchymal and Kupffer cells (2) foci of parenchymal necrosis in the periportal and midzonal areas presumably due to the effects of escaped bile (3) elongation dilatation and proliferation of the interlobular and perilobular bile ducts (4) exudation of polymorphonuclear eosinophilic and mononuclear cells in the portal triads and (5) thickening of the portal triads due to edema exudate duct proliferation and fibrosis If the obstruction is not relieved the portal triads continue to thicken and extend further and further into the parenchyma ultimately bridging adjacent portal triads and giving rise to a perilobular fibrosis At this stage the lobular pattern is still evident but extension of the fibrotic and inflammatory process to the parenchyma ultimately destroys the normal lobular pattern producing the full blown picture of biliary cirrhosis The liver is enlarged finely granular firm and bile stained Large nodules are unusual since the regenerative response of the parenchyma is limited in the face of bile stasis It should be noted that the transition from simple bile stasis to outspoken cirrhosis is a very gradual one and seldom can be recognized clinically except late in the disease

Early in *primary intrahepatic biliary cirrhosis* there is a low grade chronic inflammatory reaction centered about the small perilobular cholangioles This is accompanied by perilobular bile stasis and degenerative changes in the adjacent parenchymal cells As the disease advances fibrosis and inflammation extend into the parenchyma bridging adjacent portal triads and producing the type of perilobular fibrosis seen in early obstructive biliary cirrhosis However the reduplication of the terminal cholangioles is less striking the large interlobular ducts tend to diminish in number and evidence of bile stasis is less prominent Later as the fibrotic process progresses the lobular pattern is obliterated and the picture of cirrhosis emerges At this stage the liver is enlarged bile stained and finely granular

The evolution of the lesion in *cholangiolitic hepatitis and cirrhosis* has been described elsewhere (p 1491)

In *drug induced* biliary cirrhosis the pathogenesis of the lesions closely resembles that of the primary intrahepatic type

It should be emphasized that while it may be possible to distinguish between the lesions in the various forms of biliary cirrhosis early in the course of the disease it is rarely possible to do so by the time the full blown picture of cirrhosis has developed

The pathogenesis of the jaundice in the intrahepatic type of biliary cirrhosis is uncertain Obstruction of the cholangioles by inflammatory exudate and fibrosis and increased cholangiolar permeability with regurgitation of bile are thought to be the principal factors involved but the evidence for this is indirect and inconclusive

Clinical Features In the *primary intrahepatic type* of biliary cirrhosis the onset is insidious with pruritus or less commonly with jaundice As the disease advances pruritus becomes more troublesome jaundice deepens slowly bile appears in the urine and the stools tend to lighten in color Often these signs of biliary "obstruction" fluctuate in intensity Progressive enlargement and induration of the liver occurs and usually is accompanied by significant splenomegaly Many patients develop a striking melanotic pigmentation of the skin and occasionally this is associated with vitiligo Generalized lymphadenopathy is common and occasionally clubbing of the fingers is seen

Some months to years after onset a certain number of patients develop xanthomatosis Usually this can be correlated with a sustained elevation of the serum lipids It has been found that if the total lipids exceed 1 800 mg or if the total cholesterol exceeds 500 mg per 100 ml for a period in excess of 3 months xanthomas may be expected to appear This occurs first as typical xanthelasma of the eyelids and then as flat planus lesions in the

ascites appears the life expectancy is very much shorter and (6) therapy is far less effective

Laboratory Features The results of liver function tests are like those in Laennec s cirrhosis except that (1) the serum globulin level tends to be higher occasionally reaching concentrations of 8 or 9 Gm per 100 ml while the serum albumin level tends to be lower (2) hypocholesteremia is more common and (3) thymol turbidity is increased with greater regularity and higher values are more frequent

Treatment The principles of treatment outlined for Laennec s cirrhosis (p 1503) are equally applicable in this disease Although dietary therapy is less effective as far as recovery of the liver is concerned it is nevertheless important in maintaining the patient s nutritional status during his prolonged illness and in controlling water and salt retention Bed rest is particularly important during the early phase of the disease and during periods of acute progression ACTH and cortisone may be helpful and should be tried in all cases with evidence of active hepatocellular necrosis and inflammation Usually prolonged therapy is indicated so that the dose must be reduced to low maintenance levels as soon as maximum benefit has been achieved in order to minimize undesirable side effects

Biliary Cirrhosis

Definition While it may be difficult to differentiate between biliary and other forms of cirrhosis on morphologic grounds alone especially late in the disease the clinical manifestations and laboratory features of biliary cirrhosis are highly characteristic They include (1) the early appearance and persistence of an obstructive like jaundice with pruritus dark urine and high levels of serum alkaline phosphatase cholesterol and phospholipid (2) marked hepatomegaly (3) a tendency to develop xanthomas of the skin as the serum lipids increase progressively and (4) a relatively benign course for a number of years during which there are few if any clinical or laboratory signs of hepatocellular failure followed ultimately by terminal hepatic decompensation or massive bleeding from esophageal varices

Etiology and Classification There are two major types of biliary cirrhosis one develops following prolonged obstruction of the extrahepatic bile ducts the other is the consequence of a chronic intrahepatic inflammatory reaction due to a variety of factors some of which are still unknown These two types may be conveniently classified as follows

I Extrahepatic—due to partial or complete occlusion of the major bile ducts
II Intrahepatic
  A Primary—etiology unknown
  B Secondary—due to
    1 Viral hepatitis
    2 Drug sensitization reactions
    3 Hemochromatosis(?)

The *extrahepatic* type is seen most frequently following prolonged partial occlusion of the common *bile duct by postoperative stricture or stone* However it may be the result of congenital atresia carcinoma or benign cysts anywhere along the course of the biliary tract from the ampulla of Vater to the bifurcation of the hepatic duct in the porta hepatis provided the patient survives sufficiently long and the obstruction is not relieved There appear to be marked differences in individual susceptibility biliary cirrhosis occurring within a few months of obstruction in some instances and not for several years or not at all in others The question of whether biliary tract infection is a contributory factor is still unsettled

The *primary type of intrahepatic biliary cirrhosis* occurs almost exclusively in women Neither the etiology nor the reason for the unusual sex distribution is known However it is noteworthy that many of the patients have an allergic background and that the number of cases reported has increased since the introduction of the sulfonamides and other sensitizing drugs Since some of the latter have been implicated in the pathogenesis of the secondary type of intrahepatic biliary cirrhosis it is conceivable that unrecognized drug reactions are a more important etiologic factor in the primary type than is generally recognized Similarly unrecognized infections with the hepatitis virus may be a factor in some cases since it is known that they are capable of producing biliary cirrhosis

The secondary type of intrahepatic biliary cirrhosis appears to be the end stage of a progressive cholangiolitic hepatitis due either to the hepatitis virus (p 1491) or to drug hypersensitivity (p 1496) Thus typical cases have been reported following acute viral hepatitis and reactions to neoarsphenamine and neocinchophen and the author has seen it develop following reactions to the sulfonamides thiourea and phenobarbital Other drugs that produce a similar type of cholangiolitic hepatitis like chlorpromazine (Thorazine) and methyl testosterone have not yet been implicated but it is possible that they too will prove to be of etiologic importance

Rarely patients with hemochromatosis develop hypercholesteremia and xanthomatosis It is not known whether the hemosiderin deposits in such cases give rise to a form of biliary cirrhosis whether the lipid disturbance is merely an atypical manifestation of hemochromatosis or whether the hemosiderosis is secondary to an underlying biliary cirrhosis

At one time the primary intrahepatic type of

matory reaction The central veins are dilated and thickened and occasionally there is hemorrhage into the pericentral zone of degenerating liver cells Usually these changes are the consequence of the increase in hepatic venous pressure the stasis of blood and the hypoxia that follow congestive heart failure However very similar changes may be produced by occlusion of the hepatic veins (Chiari s syndrome) constriction of the pericardium and vascular shock

If congestion is prolonged and severe the pericentral zones of parenchymal atrophy and necrosis extend until adjacent central veins are bridged Since hepatocellular regeneration is relatively ineffective under these conditions the stroma tends to collapse forming bands of condensed and thickened reticulum fibers which ultimately undergo collagenization This gives rise to a reversal of the normal lobular pattern with centrally placed portal triads and perilobular rings of fibrous tissue joining adjacent central veins Later the zones of congestion atrophy and reticular collapse extend to the portal triads so that ultimately the lobular architecture is destroyed producing a picture which in its late stages may be indistinguishable from Laennec s cirrhosis As a rule there is little active regeneration so that the liver is finely granular and tends to diminish in size Occasionally however *particularly when bouts of severe congestion alternate* with periods of compensation regenerative nodules of varying size may be formed

Clinical Features In uncomplicated *chronic passive congestion* the liver is enlarged and tender and in long standing cases it may be firm even in the absence of fibrosis Pulsation of the liver is characteristic of tricuspid valvular disease Pressure over the liver often produces a significant increase in the distention of the jugular veins (hepatojugular reflux) Occasionally the spleen is enlarged but other signs of portal hypertension are rare although small asymptomatic esophageal varices may be observed at autopsy Many patients with congestive failure exhibit mild hyperbilirubinemia but frank jaundice and bilirubinuria are unusual except in patients with severe tricuspid valvular disease or in those with complicating pulmonary infarction The jaundice is primarily of hepatocellular origin but increased hemoly*sis may be a factor in cases with* pulmonary infarction Ascites is a common finding in advanced congestive failure No doubt the increase in hepatic venous pressure plays a role in its pathogenesis as it does in other conditions (p 148) but how much the accompanying hepatocellular injury contributes to the general phenomenon of salt and water retention in cardiac failure is still a matter of conjecture

The transition from chronic passive congestion of the liver to *cardiac cirrhosis* is a very gradual one and difficult to recognize clinically since the signs and symptoms in the two conditions are very much the same However intractable ascites a firm nontender liver absence of a demonstrable hepatojugular reflux and progressive splenomegaly are features that should suggest the diagnosis In contrast to other forms of cirrhosis deep jaundice spider nevi bleeding from esophageal varices and hepatic coma are unusual

While cardiac cirrhosis may occur in any type of heart disease it is seen most frequently in rheumatic heart disease severe cor pulmonale and constrictive pericarditis

Laboratory Features The most frequent functional abnormalities associated with congestion of the liver include Bromsulphalein retention, a slight rise in the serum bilirubin level an increase in urine urobilinogen and a fall in the serum albumin These characteristics parallel the severity of the hepatocellular changes However there is some evidence to indicate that Bromsulphalein retention may in part at least be a function of reduced hepatic blood flow In patients with overt jaundice the urine may contain bile Occasionally there is an increase in serum globulin cephalin-cholesterol flocculation and thymol turbidity

The changes in cardiac cirrhosis are very similar but the serum albumin concentration tends to fall *to a lower level*

Diagnosis The recognition of congestive hepatomegaly and cardiac cirrhosis is seldom difficult However they may be mistaken for other forms of cirrhosis when the signs of heart disease are masked as in constrictive pericarditis

Hemochromatosis

See p 718

Hepatolenticular Degeneration (Wilson s Disease)

See p 725

Cirrhosis Due to Schistosomiasis

Infestations with *Schistosoma mansoni* or *Schistosoma japonicum* may give rise to an unusual type of cirrhosis Although the disease is not indigenous to this country it is very common among Puerto Rican immigrants and is seen occasionally in Sec*ond World War veterans who served in the Pacific* area

Pathology Some of the schistosome ova deposited in the distal tributaries of the portal vein are swept back into the liver where they produce a granulomatous reaction in the portal triads the periportal parenchyma and the intrahepatic portal radicles themselves As the lesions age and become fibrotic the encapsulated ova degenerate Occasionally the process is confined to the larger intrahepatic periportal areas giving rise to so called white

palmar creases and over the skin of the neck chest and back Later more nodular tuberous lesions appear over the extensor surfaces of the knuckles elbows knees and ankles and over the buttocks

Another striking feature of this disease is steatorrhea due apparently to malabsorption of fat related to a decrease in bile salt excretion The stools tend to increase in frequency and occasionally are bulky foul and loose A more important complication is decalcification of bone which often is accompanied by compression of the vertebral bodies and back pain This appears to be the consequence of excessive fecal losses of vitamin D and calcium in relation to the steatorrhea but a postmenopausal defect in bone matrix formation may be involved in some cases It has been suggested that losses of other fat soluble vitamins and especially vitamin A may play a role in the pigmentation and thickening of the skin that occurs in this disease

In contrast to other forms of cirrhosis the patient feels remarkably well and loses little or no weight over a period of years despite the fact that the disease is progressive Also there is a striking absence of anorexia indigestion abdominal pain and tenderness chills and fever Ultimately however signs of hepatic failure (p 1501) or massive bleeding from esophageal varices appear Death may occur within 2 years but many patients live as long as 10 years Of interest is the fact that as hepatocellular failure develops there is a fall in the serum lipids and a disappearance or decrease in the size of the xanthomatous lesions

The clinical course in the other forms of biliary cirrhosis is very similar except that attacks of abdominal pain chills and fever and a history of antecedent gallbladder disease or biliary tract surgery are common in the extrahepatic type while an onset with typical acute viral hepatitis or a drug sensitization reaction is characteristic of the secondary intrahepatic type

Laboratory Features Early in the disease the principal findings are those of obstructive jaundice viz an elevated direct and total serum bilirubin a high serum alkaline phosphatase level increased serum cholesterol and phospholipid and a decrease in fecal urobilinogen Characteristically the serum is clear despite its high lipid content apparently because the concentration of neutral fat is not increased The serum albumin level is normal or only slightly decreased but falls when hepatocellular failure occurs However the serum globulins and especially the beta and gamma fractions are increased from the beginning The cephalin cholesterol flocculation reaction may be positive or negative but thymol turbidity is increased with regularity high values being especially common in patients with marked hypercholesteremia Despite steatorrhea and jaundice the prothrombin level is normal or if depressed is readily corrected by the parenteral administration of vitamin K

Diagnosis The possibility of biliary cirrhosis must be considered in any case of prolonged obstructive jaundice accompanied by significant hepatomegaly Once signs of portal hypertension or xanthomatosis appear the diagnosis can be made clinically with reasonable assurance but earlier in the disease biopsy of the liver may be necessary Usually the *most difficult problem is the distinction between* the extra and intrahepatic types Since this can seldom be made with certainty on clinical or even histologic grounds every patient with biliary cirrhosis deserves a thorough surgical exploration with cholangiography to exclude the presence of a remediable obstruction in the extrahepatic biliary tree

Treatment Surgical relief of biliary obstruction is essential in those with extrahepatic biliary cirrhosis If this can be accomplished remarkable improvement may be expected even when the disease is advanced

The objectives of treatment in the intrahepatic type of cirrhosis are the maintenance of nutrition the control and prevention of complications and the relief of pruritus

While a high protein high caloric diet is of value in maintaining weight and strength it appears to have little effect on the underlying hepatic lesion Fats need not be restricted unless steatorrhea becomes troublesome There is no evidence that limitation of dietary fat alters the course of the disease or the accompanying hypercholesteremia and xanthomatosis Daily supplements of vitamins A and D and a high calcium intake are indicated to compensate for fecal losses Vitamin K is administered if the prothrombin level is low It may be necessary to administer the fat soluble vitamins by the parenteral route if steatorrhea is severe

The management of ascites and bleeding esophageal varices is the same as in Laennec's cirrhosis (pp 1503 1504)

Pruritus is a difficult therapeutic problem Occasionally soothing lotions and baths and the antihistamine drugs are helpful but when itching is severe only methyltestosterone in daily doses of 25 mg sublingually appears to be effective Although it usually produces an increase in jaundice it has no long term ill effects Moreover it tends to lower the serum cholesterol and phospholipid levels and may thus prevent further xanthoma formation

Cardiac Cirrhosis

Pathology Characteristically the liver enlarges in congestive heart failure Microscopically there are engorgement of the pericentral sinusoids atrophy degeneration and necrosis of the intervening parenchymal cells and little or no inflam

matory reaction The central veins are dilated and thickened and occasionally there is hemorrhage into the pericentral zone of degenerating liver cells Usually these changes are the consequence of the increase in hepatic venous pressure the stasis of blood and the hypoxia that follow congestive heart failure However very similar changes may be produced by occlusion of the hepatic veins (Chiari s syndrome) constriction of the pericardium and vascular shock

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Pathology Some of the schistosome ova deposited in the distal tributaries of the portal vein are swept back into the liver where they produce a granulomatous reaction in the portal triads the periportal parenchyma and the intrahepatic portal radicles themselves As the lesions age and become fibrotic the encapsulated ova degenerate Occasionally the process is confined to the larger intrahepatic periportal areas giving rise to so-called white

pipestem fibrosis which mimics cirrhosis clinically but differs from it in that the remaining parenchyma is intact However many patients with hepatic schistosomiasis develop a fine nodular cirrhosis of the Laennec s type In some patients this appears to be the consequence of a widespread granulomatous reaction to ova but in others the etiology is uncertain and may be related to accompanying malnutrition

Clinical Features The principal findings in hepatic schistosomiasis are progressive enlargement of the liver and signs of portal hypertension Bleeding from esophageal varices is a frequent complication while signs of hepatocellular failure are relatively uncommon except in patients with malnutrition in whom the disease behaves more like Laennec s cirrhosis

Some patients have frank signs of intestinal schistosomiasis but many of the Puerto Ricans seen in this country who present with hepatomegaly or esophageal bleeding have no other clinical manifestations of the disease and often have had no exposure to infestation for many years Often rectal biopsy is positive for ova but if not the diagnosis can usually be established by means of needle biopsy of the liver

For a more complete discussion of schistosomiasis see p 1130

Rare Forms of Cirrhosis

Granulomatous Cirrhosis Occasionally granulomatous diseases are accompanied by cirrhosis In the case of sarcoidosis (p 1498) it is reasonably certain that the cirrhosis follows healing of extensive granulomatous lesions but in tuberculosis (p 1498) and brucellosis (p 1499) it is doubtful that the cirrhosis is of granulomatous origin Rarely the diffuse hepatitis of congenital syphilis gives rise to a fine diffuse fibrosis of the liver However there is no evidence that the acquired form of syphilis ever produces cirrhosis

Cirrhosis Associated with Metabolic Disorders A significant number of patients with *diabetes mellitus* have fatty livers and a few develop a lesion resembling Laennec s cirrhosis Many authorities attribute the fatty infiltration to obesity starvation or poor regulation of the diabetes and regard the association of diabetes and cirrhosis as fortuitous However this opinion is not shared by all investigators so that the pathogenesis of cirrhosis in diabetes is still an unsettled problem

Rarely *hyperthyroidism* is accompanied by cirrhosis It is generally believed that the cirrhosis is the consequence of congestive heart failure but it has been suggested that in some instances it may be the result of a specific circulatory disturbance an induced nutritional deficiency or a relative hypoxia related to the hyperthyroid state

Not infrequently infants with *galactosemia* a congenital disease in which galactose cannot be metabolized develop an hepatic lesion resembling Laennec s cirrhosis This has been attributed to the toxic action of galactose or to a nutritional deficiency related to the inability to utilize the galactose in milk However galactose does not produce hepatic injury in animals and the character of the lesions and the rapidity with which they appear in affected infants are not typical of nutritional deficiency so that neither of the theories appears tenable

Rarely *von Gierke s disease* (p 731) is associated with cirrhosis

As previously noted (p 1505) the *de Toni Fanconi syndrome* is occasionally accompanied by a coarsely nodular cirrhosis The pathogenesis of the hepatic lesion is unknown A nutritional deficiency related to the loss of amino acids has been postulated but the evidence for this is not convincing

Erythroblastosis Fetalis Often the liver is severely injured in erythroblastosis and rarely cirrhosis is a sequela On the basis of indirect evidence it has been suggested that other forms of infantile or juvenile cirrhosis may be the consequence of other unrecognized maternal blood incompatibilities

Infiltrations of the Liver

Fatty Liver Usually fatty infiltration of the liver is due to a deficiency of lipotropic substances secondary to faulty dietary habits chronic alcoholism absorptive defects or the malnutrition of certain chronic wasting diseases However it is seen also in metabolic disorders like diabetes mellitus and galactosemia in obesity and as a transient phenomenon in poisoning with agents like carbon tetrachloride and phosphorus The pathogenesis in the latter group is uncertain Except in the case of obesity long continued fatty infiltration appears to predispose to the development of cirrhosis

Often the fatty liver is enlarged to palpation and not infrequently there is mild Bromsulphalein retention Other signs of hepatocellular failure and portal hypertension do not occur unless there is accompanying hepatic necrosis or fibrosis

Hemosiderosis Usually abnormal deposits of hemosiderin in the liver are a sign of increased total body stores of iron This may be the result of an excessive uptake of iron from the gastrointestinal tract due to (1) a congenital absorptive defect as in hemochromatosis (2) the stimulus of chronic anemia with failure to utilize the absorbed iron as in certain hemolytic states (3) an excessive intake of iron (4) the use of low protein low phosphate diets that enhance iron absorption or (5) the transfusion of large amounts of blood

Uncomplicated hemosiderosis of the liver produces no symptoms The question of whether the fibrosis seen in advanced cases is the result of hepatocellular degeneration related to excessive storage of iron is still unsettled

The reader is referred to the chapter on hemochromatosis (p 718) for a more complete discussion of this subject

Glycogen Storage (von Gierke s) Disease See p 731

Amyloidosis The liver is involved in a high proportion of patients with secondary amyloidosis and somewhat less frequently in those with primary amyloidosis and the type associated with multiple myeloma Amyloid is deposited between the sinusoids and the parenchymal cells slowly obliterating the former and causing atrophy of the latter In addition the walls of the blood vessels may be infiltrated especially in the primary type

The liver is enlarged smooth and firm Jaundice spider nevi and ascites are rare except in advanced cases Portal hypertension is not a feature but the spleen may be enlarged as a result of amyloid deposition The remaining clinical signs and symptoms relate to involvement of other tissues and are described elsewhere (p 720)

Despite extensive infiltration of the liver hepatocellular function tends to be little deranged except for slight Bromsulphalein retention Hypoalbuminemia and hypercholesteremia common in advanced cases appear to be more closely related to the accompanying nephrotic syndrome Hyperglobulinemia is an inconstant finding and usually the cephalin cholesterol and thymol turbidity reactions are normal Occasionally high levels of serum alkaline phosphatase are seen

Lymphomatous and Other Reticuloendothelial Infiltrations Not infrequently the liver participates in the abnormal generalized reticuloendothelial reactions that characterize *leukemia Hodgkin s disease* and *lymphosarcoma* Whether the hepatic lesions represent infiltrations from without or a local reticuloendothelial reaction to the underlying stimulus is not clear Hepatomegaly is the principal finding apart from the other manifestations of the underlying disease and except for jaundice rarely is accompanied by other signs or symptoms of hepatocellular failure While jaundice may occur in any of these conditions it is most common in Hodgkin s disease where it usually is due to a combination of biliary obstruction and parenchymal destruction Occasionally a hemolytic process is involved

In *extramedullary hematopoesis* the liver may be enlarged owing to infiltration of the sinusoids and portal triads with megakaryocytes and immature erythrocytes and leukocytes Marked splenomegaly is an invariable accompaniment The disease represents a reversion to a fetal type of hematopoietic activity in response to aplasia or replacement of the normal bone marrow The hepatic lesions seldom give rise to any symptoms the principal manifestations being related to the underlying bone marrow disease

Gaucher s disease and *Niemann Pick disease* are hereditary disorders characterized by a generalized proliferation of abnormal reticuloendothelial cells containing lipid a cerebroside (kerasin) in the former and a phospholipid (sphingomyelin) in the latter In both diseases the liver and spleen are infiltrated with these cells resulting in hepatomegaly and splenomegaly The hepatic lesions give rise to no symptoms the clinical manifestations being due to involvement of other tissues (p 744)

Space-occupying Lesions

Primary Carcinoma of the Liver Carcinomas that arise in the liver may be derived from either the parenchymal cells or the intrahepatic bile duct epithelium and are known respectively as *hepatomas* and *cholangiomas* The former are twice as common as the latter Occasionally tumors show features of both types

Males are affected more frequently than females and the onset is more common after the age of fifty although the disease may occur in children and young adults The incidence is particularly high in areas where nutritional and parasitic disease of the liver is endemic Thus in this country primary hepatic carcinomas comprise only 2 5 per cent of all malignancies while in South Africa China and Malaya the incidence among natives ranges from 50 to 30 per cent

Cirrhosis appears to be an important predisposing factor and is found in approximately 75 per cent of patients with hepatoma and 50 per cent of those with cholangioma While the incidence of primary hepatic carcinoma is only 0 3 per cent in routine autopsies it is approximately 4 per cent in the cirrhotic group and almost twice that in hemochromatosis

Often the clinical picture is that of the underlying cirrhosis so that the presence of a complicating hepatoma may be overlooked In the person known to have cirrhosis the possibility of this complication should be considered when (1) jaundice ascites or bleeding from esophageal varices occurs without provocation in a patient without previous signs of hepatic decompensation, (2) abdominal pain is a prominent feature (3) the liver is unusually large and tender has large palpable nodules on its surface is enlarged asymmetrically or has an overlying friction rub or vascular bruit (4) there is rapid weight loss out of keeping with the dietary intake (5) high fever and leukocytosis are present

(6) the serum alkaline phosphatase level is unusually high or (7) the ascitic fluid is bloody It must be emphasized that these features are not seen in all cases and indeed some are relatively uncommon Jaundice occurs in only half the patients and may be due to obstruction of bile ducts or to extensive destruction of the parenchyma Ascites and esophageal bleeding are frequent but inconstant features While they may be related to the accompanying cirrhosis the tendency of the tumor to invade the hepatic and portal veins appears to be an important factor in many cases High fever marked leukocytosis friction rubs and bruits are *unusual but are important clues* when present A high alkaline phosphatase level is not a constant finding but is highly suggestive of intrahepatic malignancy particularly in the absence of jaundice Bloody ascitic fluid is seen occasionally in uncomplicated Laennec s cirrhosis but is more common in the presence of malignancy

In the absence of overt signs of cirrhosis the diagnosis may be very difficult since cachexia abdominal pain jaundice ascites and hepatomegaly are features common to other forms of intra-abdominal malignancy with metastases to the liver and peritoneum There is a clinical impression that hepatomas rarely metastasize However this is not borne out by autopsy studies which indicate that metastases occur in approximately 65 per cent of cases the sites of predilection being the periportal and peripancreatic lymph nodes the lungs and pleura the peritoneum the bones the brain and the adrenal glands Occasionally symptoms referable to bony metastases are the first to appear

Needle biopsy of the liver is an important diagnostic aid and is positive in a high proportion of cases X ray studies are useful in excluding primary carcinomas in other sites and occasionally are helpful in establishing the presence of an intrahepatic mass by demonstrating a localized elevation *of the right leaf of the diaphragm*

The outlook is virtually hopeless most patients dying within a few months to a year Successful excision of carcinoma localized to a single lobe *has been reported but this is a rarity since the* tumor has usually spread by way of the intrahepatic vessels to involve the entire liver by the time the disease is recognized clinically

Other Primary Tumors of the Liver *Hemangiomas* are the most common tumors encountered in the liver Usually they are small and asymptomatic but occasionally they are large or very numerous *producing* hepatic enlargement or localized swelling of the liver Females are affected more frequently than males and left lobe involvement is more common than right When the tumor is large it may produce pain or may give rise to a fatal hemorrhage into the peritoneal cavity either spontaneously or following trauma Occasionally obstructive jaundice is a complication and rarely congestive heart failure is the result of extensive arteriovenous shunting of blood through the tumor An hepatic bruit is audible in some cases and not infrequently calcification is demonstrable radiographically *Successful* surgical removal of localized hemangiomas is possible and is generally recommended to prevent massive hemorrhage and to relieve pressure symptoms

Malignant *hemangioendotheliomas* and other forms of *sarcoma* are very rare

Metastatic Neoplasms of the Liver These occur at least twenty times as frequently as primary carcinoma of the liver and they constitute a more important problem since hepatic metastases are found in approximately one third of all malignancies

The liver appears to provide a peculiarly favorable environment for the growth of tumor cells and by virtue of its double circulation is in a strategic position to trap metastasizing cells gaining access to either the portal venous or hepatic arterial blood stream In addition retrograde invasion of its lymphatics from adjacent organs is possible As might be expected malignancy arising in the distribution of the portal vein such as gastrointestinal and pancreatic carcinoma metastasizes to the liver more commonly than to the lung However it is surprising to find that the same is true of tumors arising in the breast uterus ovary and kidneys whose venous drainage reaches the lungs first Only in the case of thyroid and prostatic carcinoma is pulmonary involvement more common Whether tumor cells pass through the lung and reach the liver by way of the arterial circulation or extend to contiguous tissues drained by the portal vein is uncertain In the case of the breast it is believed that metastasis occurs by way of lymphatics

Metastases are usually multiple and once implanted tend to grow rapidly invading blood vessels and lymphatics and extending to other parts of the liver Not infrequently the growth of tumor tissue in the liver is far more conspicuous than at the primary site and indeed the clinical manifestations may be predominantly hepatic at a time when the primary lesion is not detectable This is particularly true of carcinomas arising in the pancreas gallbladder kidney and lung and of melanosarcomas

The clinical features vary depending on the extent and location of the lesion At one extreme there may be no signs or symptoms suggestive of metastasis while at the other invasion may be so extensive that signs of hepatocellular failure and portal obstruction are produced In general however the latter are uncommon even when widespread hepatic metastases are present

Sooner or later weight loss anorexia abdominal pain and hepatomegaly develop Usually the liver is very hard because of the fibrotic reaction frequently associated with malignant infiltration, and often nodules are palpable Although the liver is not palpable in all instances it tends to enlarge progressively as the disease advances and occasionally it grows to tremendous size Rarely an overlying friction rub may be audible Jaundice is an inconstant and late finding and may be due to obstruction of major bile ducts, either within the liver or at the porta hepatis or less commonly to hepatocellular failure Usually ascites follows spread of the tumor to the peritoneum but it may be the result of invasion of the hepatic or portal vein, severe hypoalbuminemia or hepatic decompensation Splenomegaly occurs in 10 to 15 per cent of cases It is said to be especially common in pancreatic carcinoma because of splenic vein obstruction but in the writer's experience splenomegaly has not been limited to this particular type of tumor and usually has been due to massive invasion of the liver producing portal hypertension Esophageal varices and massive upper gastrointestinal bleeding have been complications in a few such cases

Hepatocellular function may be completely normal, even in the face of extensive metastasis However Bromsulphalein retention and a significant elevation of serum alkaline phosphatase are common findings Usually cephalin-cholesterol flocculation and thymol turbidity are normal except very late in the disease Often the serum albumin level is lowered, but this may be the consequence of malnutrition The high alkaline phosphatase level is of particular diagnostic significance in the absence of jaundice and signs of bone involvement it should suggest the possibility of hepatic malignancy or some other type of infiltration

Short of surgical exploration needle biopsy of the liver is by far the most useful and accurate diagnostic aid in this disease Approximately 80 per cent of hepatic metastases can be demonstrated by this technique not infrequently in the absence of any overt signs of the disease Considering the focal character of the gross lesions seen at the autopsy and their scattered distribution this incidence appears incredible However the infiltration usually is much more diffuse than is evident on macroscopic examination because of the tendency of the tumor to spread along vascular channels

Amebic Abscess See p 1109

Pyogenic Abscess The incidence of pyogenic abscess which has always been lower than that of the amebic variety has declined appreciably since the introduction of antibiotic therapy in the management of infections that predispose to abscess formation

Almost always pyogenic abscess of the liver is the result of parenchymal invasion by organisms stemming from an adjacent or distant septic focus However the source of infection may be difficult to detect and rarely the infection is primary in the liver as a result of a penetrating or crushing wound Organisms may gain access to the liver via the portal vein hepatic artery or lymphatics or by direct extension from the biliary tract or other contiguous structures

Any suppurative focus in the drainage area of the portal vein may give rise to an hepatic abscess At one time acute appendicitis was the most frequent offender but it has been superseded by biliary tract infection probably because the latter is less amenable to chemotherapy Usually there is an initial local thrombophlebitis from which organisms are fed into the liver either by embolization or by direct extension of the phlebitic process to the portal vein and its intrahepatic radicles (pylephlebitis)

Direct extension of infection to the hepatic parenchyma occurs most commonly in suppurative cholangitis associated with biliary obstruction, but it may also follow rupture of the gallbladder perforation of a peptic ulcer pancreatic abscess or other conditions leading to subhepatic or subphrenic suppuration No doubt spread of infection by way of the lymphatics or portal radicles is an additional factor in many such cases

Rarely pyogenic infections are the result of bacterial embolization by way of the hepatic artery in hematogenous infections associated with osteomyelitis bacterial endocarditis or pulmonary disease

The lesions may be single or multiple the latter occurring more frequently when the infection has spread by way of the biliary tract or the vessels Occasionally small abscesses coalesce to form a large solitary lesion The right lobe is involved more often than the left

Most pyogenic abscesses of the liver are due to infection with *E coli* streptococci, staphylococci or Friedlander's bacilli but occasionally *Cl welchii Pseudomonas aeruginosa Salmonella* gonococci *Bacteroides funduliformis* and other agents are implicated

The principal symptoms are those of sepsis namely recurrent chills and fever sweats prostration, anorexia, nausea, vomiting and weight loss In addition there are signs pointing to involvement of the liver including abdominal pain distention and hepatic enlargement and tenderness Usually the pain is aching in character and localized over the hepatic area or epigastrium and not infrequently it radiates to the right shoulder and is aggravated by respiration Percussion and compression of the liver are painful Occasionally a large abscess may be palpable as a localized mass beneath

(6) the serum alkaline phosphatase level is unusually high or (7) the ascitic fluid is bloody It must be emphasized that these features are not seen in all cases and indeed some are relatively uncommon Jaundice occurs in only half the patients and may be due to obstruction of bile ducts or to extensive destruction of the parenchyma Ascites and esophageal bleeding are frequent but inconstant features While they may be related to the accompanying cirrhosis the tendency of the tumor to invade the hepatic and portal veins appears to be an important factor in many cases High fever marked leukocytosis friction rubs and bruits are unusual but are important clues when present A high alkaline phosphatase level is not a constant finding but is highly suggestive of intrahepatic malignancy particularly in the absence of jaundice Bloody ascitic fluid is seen occasionally in uncomplicated Laennec s cirrhosis but is more common in the presence of malignancy

In the absence of overt signs of cirrhosis the diagnosis may be very difficult since cachexia abdominal pain jaundice ascites and hepatomegaly are features common to other forms of intraabdominal malignancy with metastases to the liver and peritoneum There is a clinical impression that hepatomas rarely metastasize However this is not borne out by autopsy studies which indicate that metastases occur in approximately 65 per cent of cases the sites of predilection being the periportal and peripancreatic lymph nodes the lungs and pleura the peritoneum the bones the brain and the adrenal glands Occasionally symptoms referable to bony metastases are the first to appear

Needle biopsy of the liver is an important diagnostic aid and is positive in a high proportion of cases X ray studies are useful in excluding primary carcinomas in other sites and occasionally are helpful in establishing the presence of an intrahepatic mass by demonstrating a localized elevation of the right leaf of the diaphragm

The outlook is virtually hopeless most patients dying within a few months to a year Successful excision of carcinoma *localized to a single lobe* has been reported but this is a rarity since the tumor has usually spread by way of the intrahepatic vessels to involve the entire liver by the time the disease is recognized clinically

Other Primary Tumors of the Liver *Hemangiomas* are the most common tumors encountered in the liver Usually they are small and asymptomatic but occasionally they are large or very numerous producing hepatic enlargement or localized swelling of the liver Females are affected more frequently than males and left lobe involvement is more common than right When the tumor is large it may produce pain or may give rise to a fatal hemorrhage into the peritoneal cavity either spontaneously or following trauma Occasionally obstructive jaundice is a complication and rarely congestive heart failure is the result of *extensive arteriovenous shunting* of blood through the tumor An hepatic bruit is audible in some cases and not infrequently calcification is demonstrable radiographically Successful surgical removal of localized hemangiomas is possible and is generally recommended to prevent massive hemorrhage and to relieve pressure symptoms

Malignant *hemangioendotheliomas* and other forms of *sarcoma* are very rare

Metastatic Neoplasms of the Liver These occur at least twenty times as frequently as primary carcinoma of the liver and they constitute a more important problem since hepatic metastases are found in approximately one third of all malignancies

The liver appears to provide a peculiarly favorable environment for the growth of tumor cells and by virtue of its double circulation is in a strategic position to trap metastasizing cells gaining access to either the portal venous or hepatic arterial blood stream In addition retrograde invasion of its lymphatics from adjacent organs is possible As might be expected malignancy arising in the distribution of the portal vein such as gastrointestinal and pancreatic carcinoma metastasizes to the liver more commonly than to the lung However it is surprising to find that the same is true of tumors arising in the breast uterus ovary and kidneys whose venous drainage reaches the lungs first Only in the case of thyroid and prostatic carcinoma is pulmonary involvement more common Whether tumor cells pass through the lung and reach the liver by way of the arterial circulation or extend to contiguous tissues drained by the portal vein is uncertain In the case of the breast it is believed that metastasis occurs by way of lymphatics

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the costal margin or may cause fullness and tenderness of the intercostal spaces When the abscess is located high in the right lobe secondary involvement of the diaphragm and pleura may ensue giving rise to cough splinting of the chest pleural effusion and signs of atelectasis On x ray examination the diaphragm is elevated and fixed the cardiophrenic angle is blunted and occasionally a local bulge can be made out If a gas producing organism is present it may be possible to demonstrate fluid levels within the abscess Jaundice is not a prominent feature except in multiple abscess associated with suppurative cholangitis or pylephlebitis Usually its presence denotes a grave prognosis

In addition to the signs of hepatic abscess there may be others related to (1) the underlying source of infection such as acute appendicitis (2) concomitant metastatic suppurative foci in the lungs spleen kidney or brain or (3) any of the complications of hepatic abscess including peritonitis subphrenic abscess empyema lung abscess and bronchohepatic fistula

Usually the patient is acutely ill but solitary abscesses may encapsulate and run a more indolent course characterized by low grade fever sweats wasting and abdominal pain

Marked leukocytosis and an increase in the percentage of polymorphonuclear cells are the outstanding laboratory features Liver function test results may be normal but in patients with jaundice the concentrations of serum bilirubin and alkaline phosphatase are increased With prolonged infection the serum albumin level falls and the globulin rises

Most pyogenic abscesses of the liver can be prevented by prompt use of antibiotics and appropriate surgical measures in the treatment of intraabdominal infections Once the abscess has developed surgical drainage and intensive antibiotic therapy are indicated Unfortunately drainage is seldom successful when multiple abscesses are present However in those abscesses associated with suppurative cholangitis drainage of the extrahepatic bile ducts may be effective

Gumma Gummas the necrotic masses of conglomerate granulomas seen in late syphilis are rare at present In the liver they give rise to deep scars as they heal and if multiple may produce the type of deformity known as *hepar lobatum* Solitary lesions seldom produce symptoms However hepar lobatum while not a form of cirrhosis since the lobular pattern of the remaining parenchyma is normal occasionally produces signs of portal hypertension ascites and jaundice Pain and low grade fever are prominent in some cases Usually the liver is palpable and coarsely nodular Predominant involvement of the left lobe is said to be characteristic but this is denied by many authorities Liver function is little deranged except terminally

Echinococcus Cyst See p 1139

Polycystic Disease As a result of a congenital developmental defect isolated segments of the intrahepatic bile ducts may undergo cystic change within the trabeculae of the liver The cysts vary in size and number and if numerous may cause great enlargement and honeycombing of the liver In approximately half the cases there are associated *polycystic lesions in other organs including the* kidney spleen pancreas and lungs

As a rule hepatic cysts give rise to no symptoms Occasionally however the liver enlarges during middle age and by exerting pressure on adjacent structures produces pain and gastrointestinal symptoms Rarely portal hypertension is a complication

Functional Disorders of Unknown Etiology

Constitutional Hyperbilirubinemia (Synonyms *congenital hyperbilirubinemia familial nonhemolytic jaundice chronic intermittent juvenile jaundice Gilbert's cholémie simple familiale*) This condition is characterized by a mild intermittent jaundice without other evidence of hepatic or hemolytic disease which often is accompanied by lassitude and vague gastrointestinal complaints It occurs at all ages but is most frequent in young adults Excessive fatigue overindulgence in alcohol infection and surgical trauma appear to be the factors most commonly involved in precipitating relapses Usually there are no physical findings of note although slight hepatomegaly is seen in some cases The serum bilirubin level seldom rises above 5 mg per 100 ml and characteristically the increase is in the indirect reacting fraction as in hemolytic jaundice However there is no increase in urine or fecal urobilinogen reticulocytosis or other evidence of increased hemolysis No bilirubin is excreted in the urine and the color of the stools remains normal Except for the hyperbilirubinemia no other abnormalities of hepatic function can be demonstrated and a cholecystogram usually reveals a normal gallbladder On histologic examination the liver appears to be normal although occasionally a mild degree of fatty infiltration may be found

Although the symptoms recur over a period of years they tend to regress with advancing age and never are followed by signs of progressive hepatic disease As a rule there is little disability but often the jaundice is a matter of great concern to both the patient and his physician unless its nature is recognized

The jaundice appears to be due to a reduction in the capacity of the otherwise normal parenchymal cells to excrete bilirubin Recent evidence indicates

that this is related to an enzymatic defect partially blocking the conversion of indirect reacting bilirubin to its glucuronide Since other members of the family are similarly affected in approximately half the cases that are recognized it is believed that the defect is inherited as a dominant characteristic However it should be noted that a very similar syndrome may follow an attack of acute viral hepatitis so that the enzymatic defect may be acquired in some instances

Unfortunately this syndrome is not well known to clinicians so that often it is mistaken for relapsing hepatitis or hemolytic icterus The features that should suggest the diagnosis include a mild hyperbilirubinemia of the indirect type absence of clinical or laboratory evidence of liver disease absence of signs of increased hemolysis and a benign relapsing clinical course Occasionally liver biopsy is needed for confirmation

Attempts to treat this disease with cortisone and ACTH have been unsuccessful

Chronic Idiopathic Jaundice with Pigmentation of the Liver (Dubin Johnson Syndrome) As in constitutional hyperbilirubinemia this disease affects young individuals and is characterized by a chronic intermittent jaundice However in contrast the increase in serum bilirubin is of the direct reacting type there are other associated abnormalities of hepatic function and histologically the liver shows a curious type of pigmentation which is pathognomonic

Usually the onset is insidious but in approximately a third of the patients it is acute and simulates an attack of acute viral hepatitis The chief complaints are jaundice right upper quadrant pain anorexia nausea vomiting weakness and fatigability The liver may be enlarged and tender and when inspected during surgical exploration appears dark brown or green black in color On histologic examination a highly characteristic coarsely granular brown pigment is found in the centrilobular parenchymal cells The nature of this pigment is not known but it does not appear to be bilirubin hemosiderin ceroid or any of the known lipochromes It has been suggested that it may be a derivative of bilirubin a dipyrrolic breakdown product of hemoglobin or an oxidation product of polymerized unsaturated fatty acids Usually the liver shows no other abnormalities although the portal triads may contain a small number of mononuclear cells

The principal laboratory findings are a slight to moderate increase in serum bilirubin and a mild degree of Bromsulphalein retention Approximately half the bilirubin reacts directly Often at the height of the jaundice the urine contains bile and an increased amount of urobilinogen Occasionally cephalin cholesterol flocculation and thymol turbidity are abnormal but usually the levels of serum protein cholesterol and alkaline phosphatase remain within normal limits On cholecystography the gallbladder fails to fill with dye

In the small number of cases reported thus far there has been no evidence of progressive hepatic damage although the disease has shown no tendency to abate over a period of years

It has been suggested that the disease is due to an inborn error in metabolism leading to a defect in the capacity of the liver to excrete bilirubin Bromsulphalein cholecystography dyes and the unusual pigment found in the liver However there is no evidence that the disease is either congenital or hereditary and the possibility that the excretory defect is acquired as a result of viral hepatitis or other inflammatory disease of the liver has not been excluded

It is difficult if not impossible to differentiate this condition from the various forms of chronic hepatitis and low grade extrahepatic biliary obstruction on clinical grounds alone so that liver biopsy is essential for diagnosis

Familial Nonhemolytic Jaundice in the Newborn Crigler and Najjar have described a rare form of jaundice in newborn infants which is characterized by a high level of indirect reacting bilirubin in the serum and the frequent occurrence of kernicterus as in erythroblastosis fetalis However in contrast there is no evidence of increased hemolysis Except for the inability to excrete bilirubin, hepatic function is not altered and histologically the liver appears normal but usually shows bile thrombi in the canaliculi The prognosis is grave most affected infants dying within the first year of life

Thus far all the cases recognized have had a common ancestor suggesting that the disease is hereditary and possibly due to a genetically determined disturbance in the excretory function of the hepatic parenchyma In many respects the disease resembles familial hyperbilirubinemia but the striking differences in incidence age distribution central nervous system involvement and prognosis suggest that the two conditions are unrelated

HEPATOBILIARY DISEASE

Extrahepatic Biliary Obstruction Any obstruction to the outflow of bile from the ampulla of Vater to the bifurcation of the common hepatic duct at the hilum of the liver will result in jaundice Since the excretory capacity of the liver for bilirubin greatly exceeds the normal demands made upon it uncomplicated occlusion of the right or left hepatic duct alone does not produce jaundice The pathogenesis of the jaundice and the nature of the associated hepatic lesions have been described elsewhere (p 145)

The most frequent causes of obstruction include stone stricture congenital atresia carcinoma of the bile duct and carcinoma of the head of the pancreas Extrinsic pressure by malignant cystic or inflammatory masses enlarged hepatic hilar lymph nodes or inflammatory reactions in the pancreas may constrict the duct but this occurs less frequently than is generally believed Even in the case of carcinoma of the head of the pancreas invasion of the duct wall appears to be a more important factor than extrinsic pressure Choledochal cyst and invasion of the biliary tree by *Ascaris lumbricoides* are rare causes of obstructive jaundice

The obstruction is rarely complete except in the case of congenital atresia and malignancy and even in the latter it may be incomplete for some time and may fluctuate in degree as a result of inflammatory swelling and necrosis of the tumor

Usually the *onset* of obstructive jaundice is gradual but it may be sudden when the common duct is occluded by stone or when a partial obstruction is complicated by an acute cholangitis Nevertheless the jaundice rarely deepens with the rapidity seen in acute viral hepatitis since the interruption of bile flow is seldom so sudden or complete The depth of jaundice ultimately attained depends on the degree and duration of the obstruction and to some extent on the presence or absence of complicating cholangitis and hepatocellular injury The most intense forms of jaundice are seen in malignant obstruction and not infrequently are associated with a greenish tint to the skin and sclerae due to the presence of biliverdin The course of the jaundice is variable depending on the nature of the obstruction However it seldom follows the regular pattern seen in acute viral hepatitis (p 1488)

Pruritus is a common feature but is not pathognomonic of obstructive jaundice occurring as a transient phenomenon in viral hepatitis and as a more persistent symptom in primary hepatic biliary cirrhosis Usually the *urine darkens* because of the presence of bilirubin and if the obstruction is reasonably complete the *stools* become *clay colored*

If the obstruction is sustained the *liver enlarges* and may be *tender* Often in carcinomatous obstruction of the common duct the *gallbladder* is *distended* and *palpable* This is unusual when stone or stricture is present since the gallbladder is apt to be contracted as a result of chronic inflammation and scarring (Courvoisier s law) Occasionally the gallbladder is palpable because it contains numerous large stones is distended by an impacted stone in the cystic duct (hydrops) or is the site of carcinomatous infiltration Splenomegaly is unusual except when the obstruction is due to carcinoma of the pancreas or is associated with extensive intrahepatic metastases

Fever particularly if accompanied by recurrent *chills* usually indicates the presence of a complicating ascending cholangitis However it may be related to an underlying malignancy

Pain is an inconstant feature in obstructive jaundice and may be due to the presence of stone acute cholangitis carcinoma or other complicating disease The occurrence of typical biliary colic almost always points to a common duct stone However not infrequently stones produce obstruction without inducing pain In acute cholangitis which may accompany either a common duct stone or a stricture the pain tends to be more constant and is located either in the epigastrium or over the liver itself As a rule the onset of carcinomatous obstructive jaundice is painless but frequently as the disease progresses and the underlying tumor invades adjacent structures pain is produced

Other clinical and diagnostic features related to the specific diseases that give rise to obstructive jaundice are described in the chapter that follows

The principal *laboratory features* include hyperbilirubinemia with a high proportion of the direct reacting fraction bilirubinuria and significant elevation of the serum alkaline phosphatase and cholesterol levels Fecal urobilinogen is decreased and if the obstruction is complete as in carcinoma the daily excretion is less than 5 mg Usually urine urobilinogen is decreased or absent but if cholangitis is present it may be increased owing to the production and reabsorption of urobilinogen in the biliary tract Cephalin cholesterol flocculation and thymol turbidity are normal early in uncomplicated biliary obstruction but often they are abnormal and may be accompanied by hypoalbuminemia and hyperglobulinemia when acute cholangitis is present or when the obstruction is prolonged These changes relate both to infection and to hepatocellular injury The prothrombin concentration tends to fall it will usually rise following the parenteral administration of vitamin K

Acute cholangitis biliary cirrhosis and hepatic abscess are the chief complications of biliary obstruction

Once the diagnosis of extrahepatic biliary obstruction is firmly established the *treatment* of choice is surgical relief of the obstruction and antibiotic therapy for any accompanying inflammatory process A brief period of watchful waiting is warranted in the case of common duct stone since the latter may pass spontaneously and in the case of certain inflammatory obstructive lesions such as pancreatitis which may subside spontaneously or following appropriate chemotherapy Conservative therapy is indicated also in patients with common duct stricture who have been subjected to repeated plastic procedures and who are not likely to benefit from further attempts at repair Not infrequently the obstructive symptoms in such cases are due to a

superimposed cholangitis which may respond to antibiotics

Cholangitis Acute cholangitis of bacterial origin is almost always a complication of (1) bile stasis due to extrahepatic biliary obstruction by stone stricture or carcinoma (2) spread of infection from adjacent structures such as the gallbladder and pancreas (3) enteric infections like typhoid and paratyphoid fever or (4) parasitic invasion of the bile ducts with *A lumbricoides* liver flukes (*Clonorchis sinensis* and *Fasciola hepatica*) or *Giardia lamblia* Common duct stone is by far the most frequent cause of acute cholangitis while enteric infections and parasitic infestations are of little etiologic importance in this part of the world The relationship between cholangitis and pancreatitis is a curious one since each may be a complication of the other As a result, it may be difficult in any given case to determine which is the primary disorder

Escherichia coli and enterococci are the organisms most frequently recovered from infected bile ducts but a wide variety of other bacteria are capable of inducing acute cholangitis Most infections appear to be of the ascending type organisms gaining entrance to the common duct in the duodenum However hematogenous infections are known to occur and are of special importance in bacteremic diseases like typhoid and paratyphoid fever

It is doubtful that acute cholangitis occurs as a primary disease of the bile ducts In the curious syndrome known as *cholangitis lenta* it is alleged that the protracted *Streptococcus viridans* bacteremia which characterizes the disease is the result of a primary infection of a previously normal biliary tract However in most cases that have been investigated thoroughly an underlying biliary stone or tumor has been found

Often extrahepatic biliary obstruction is accompanied by an inflammatory reaction within the walls of the ducts and their supporting stroma in the liver even when there is no accompanying infection (p 145) Similar but less acute reactions are seen in chronic cholecystitis and a wide variety of nonbacterial hepatocellular diseases Often these are classified on an anatomic basis as forms of cholangitis However the term as used clinically implies a bacterial infection of the bile ducts often accompanied by a purulent exudate

Chills fever and jaundice are the outstanding *clinical features* in acute cholangitis Jaundice is not a constant finding, although an increase in serum bilirubin can almost always be demonstrated When present it may be due to (1) an underlying calculous or malignant biliary obstruction (2) increase of a previously asymptomatic partial occlusion by inflammatory edema or (3) hepatocellular injury as a result of the infection spreading to the parenchyma Often the liver enlarges and is painful but biliary colic is unusual except in those with an underlying common duct stone Anorexia nausea and vomiting are frequent complaints

If the cholangitis is secondary to an unrelieved partial biliary obstruction and especially a common duct stone chills and fever may recur at intervals of a few days to a few weeks a syndrome known as Charcot s intermittent biliary fever

Bacteremia liver abscess and pylephlebitis are the major complications Rarely chronic infection leads to contracture and occlusion of the extrahepatic bile ducts

Laboratory studies usually reveal marked leukocytosis hyperbilirubinemia bilirubinuria and a high serum alkaline phosphatase level Often the latter is present even in the absence of jaundice and this may be of considerable diagnostic value

Treatment depends on the underlying etiology but in general consists of surgical relief of biliary obstruction and the administration of antibiotics

VASCULAR DISEASE OF THE LIVER

Chronic Passive Congestion See p 1509

Occlusion of the Hepatic Veins (Budd Chiari Syndrome) The hepatic veins may be occluded by thrombus or tumor arising either locally or by extension from the inferior vena cava Rarely a congenital or acquired stricture is responsible

Hepatic vein thrombosis may be the result of (1) hepatic cirrhosis suppuration or malignancy (2) congenital stricture (3) polycythemia (4) crushing injury to the abdomen (5) local or generalized phlebitis (6) poisoning with senecio a weed found in South Africa or (7) thrombosis of the inferior vena cava secondary to intraabdominal suppuration malignancy or trauma Occlusion of the hepatic veins by tumor usually follows carcinomatous invasion of the vessels either directly from the liver or indirectly by way of the inferior vena cava from the kidney

The changes produced in the liver are those of severe congestion or cardiac cirrhosis (p 1509) depending on the duration of the disease

The *clinical course* is variable depending on the extent of the occlusion the rapidity with which it develops and the nature of the underlying etiology Occasionally the onset is abrupt with abdominal pain, vomiting progressive enlargement and tenderness of the liver and rapid accumulation of ascites Jaundice is an inconstant finding and when present is mild Patients with an acute and complete occlusion may go on to shock and die within a few days Others may survive for months or even years In the more chronic form of the disease ascites hepatomegaly and signs of portal hypertension predominate Ultimately the patient dies of hepato-

cellular failure mesenteric thrombosis hemorrhage from esophageal varices or as a result of the underlying disease responsible for the thrombosis Signs of inferior vena caval obstruction may antedate or accompany those pointing to occlusion of the hepatic veins

Occasionally hepatic vein thrombosis is discovered as an incidental finding at autopsy in individuals who allegedly have had no symptoms Presumably incomplete occlusion recanalization of the thrombus and the development of a collateral circulation account for the absence of symptoms in such cases

The *laboratory findings* are very much like those in chronic passive congestion and cardiac cirrhosis

Occlusion of the Portal Vein Most occlusions of the portal vein are the result of thrombosis but a few are of congenital origin due either to anomalous development of the vein or to neonatal extension of the obliterative fibrotic process in the ductus venosus and umbilical vein to the portal vein Occasionally the portal vein is replaced by a mass of thin walled vessels a condition known as *cavernomatous transformation* When it occurs in young individuals it usually is regarded as a congenital anomaly resulting from failure of the portal vein to canalize normally However since recanalization of an obstructed portal vein and the development of centripetal collateral vessels produces a similar picture cavernomatous transformation of the portal vein may represent an acquired anomaly even in children

Usually *acute thrombosis* is a complication of suppurative pylephlebitis or of surgical manipulation of the portal vein during splenectomy or porta caval anastomosis Less commonly it occurs during the course of a prolonged febrile illness such as typhoid fever or following abdominal trauma *Chronic thrombosis* which is more common is seen in approximately 10 per cent of cirrhotic patients and may be a complication of polycythemia vera or of carcinomatous invasion of the vein from any of the structures that it drains

The principal *clinical manifestations* relate to the development of portal hypertension and congestion In addition there may be signs pointing to the underlying disease responsible for the thrombosis The liver is not affected by the thrombosis per se but may be involved as a result of other concomitant factors

In acute thrombosis the early signs include abdominal pain ileus vomiting and diarrhea Later there may be ascites and splenomegaly and if the thrombosis spreads to the tributaries of the portal vein gastrointestinal infarction may ensue resulting in hematemesis melena and peritonitis

The signs of chronic thrombosis are those of portal hypertension which have been discussed elsewhere (p 149) Often the occurrence of thrombosis is overlooked particularly in patients with an underlying cirrhosis The possibility of this complication should be considered whenever sudden ascites or hematemesis occurs in a previously well compensated case of cirrhosis

Acute Pylephlebitis Acute bacterial infections of the portal vein are always secondary to suppurative foci in tissues drained by its tributaries or to suppuration in contiguous structures As previously noted (p 1513) acute appendicitis and biliary tract infections are the most common causes

The portal vein and its intrahepatic radicles show an acute inflammatory reaction and not infrequently contain pus or thrombi Hepatic abscess peritonitis and septicemia are common complications

The *clinical features* resemble those of pyogenic hepatic abscess and include chills fever nausea and vomiting abdominal pain and enlargement and tenderness of the liver Jaundice is an inconstant finding and if present is usually mild Signs of hepatic abscess or acute portal vein thrombosis may complicate the picture

Recovery may follow antibiotic therapy and surgical drainage of septic foci but the mortality rate is still high in the suppurative type of pylephlebitis Portal thrombosis and hypertension may be important sequelae

Cruveilhier Baumgarten Syndrome The outstanding feature in this condition is a periumbilical or epigastric venous bruit often accompanied by a thrill and usually associated with dilatation of the abdominal veins especially around the umbilicus where they form a rosette of vessels known as a *caput medusae*

Originally it was believed that the syndrome was always due to a congenital anomaly characterized by patency of the umbilical vein hypoplasia of the portal vein and secondary atrophy of the liver However it is now known that the dilated vessels and bruit usually are due to a greatly increased venous collateral circulation reaching the abdominal wall by way of the falciform ligament as a result of an acquired portal hypertension Both the umbilical and paraumbilical veins may participate in this process The syndrome occurs most frequently *in cirrhosis but may be seen in any other form of* portal hypertension

To distinguish between the congenital type due to failure of the umbilical vein to close and the acquired type related to portal hypertension it is customary to designate the former as Cruveilhier Baumgarten *disease* and the latter as the Cruveilhier Baumgarten *syndrome* However some authorities believe that the condition is always the result of portal hypertension and that patency of the

umbilical vein in the congenital type is the result rather than the cause of the associated hypoplasia of the portal vein.

Table 130. CHEMICAL AGENTS AND DRUGS KNOWN TO PRODUCE HEPATITIS IN MAN

Agent	Mode of action		
	Toxipathic	Sensitization	Virus carrier
Industrial and plant poisons			
Carbon tetrachloride	+		
Chlorinated naphthalenes and diphenyls	+		
Mushroom poison (*Amanita phalloides*)	+		
Phosphorus	+		
Senecio (ragwort poison)	+		
Tetrachlorethane	+		
Toluene	±		
Trinitrotoluene	+		
Anesthetic agents			
Chloroform	+		
Divinyl ether	?		
Ether (diethyl ether)	±		
Tribromethanol (Avertin)	?		
Antiarthritic agents			
Cinchophen and related derivative		+	
Gold compound		+	?
Phenylbutazone (Butazolidin)		+ (rare)	
Antibiotics			
Chloramphenicol (Chloromycetin)		(rare)	
Chlortetracycline (Aureomycin)	± (+large doses I.V.)		
Oxytetracycline (Terramycin)	±		
Penicillin		+ (rare)	+
Streptomycin		(rare)	(rare)
Anticonvulsants and sedatives			
Chlorpromazine (Thorazine)		+	
Dilantin (sodium diphenylhydantoinate)		+	
Phenobarbital		+	
Phenurone (phenacetylurea)		+	
Tridione (trimethadione)		+ (rare)	
Chemotherapeutic agents used in infection			
Antimonials (pentavalent)	?		?
Arsenicals (inorganic)	+		
Arsenicals (organic)	+	+	+
Atabrine	?	+	
Bismuth compounds			+
Isoniazid and iproniazid	P	+	
Para-aminosalicylic acid		+	
Pyrazinamide (Aldinamide)	P	?	
Stilbamidine and related derivatives of stilbene	?		
Sulfonamides	+	+	
Chemotherapeutic agents used in malignant disease			
Nitrogen mustard	?		
Urethan	+		
Hormonal and metabolic agents			
Dinitrophenol		+	
Methyltestosterone			
Thiouracil and related compounds		+	
Tapazole (methimazole)		+ (rare)	

+—frank hepatitis

±—minor hepatic injury

P—potential hazard; produces injury in animals, but not as yet reported in man.

?—produces hepatitis; pathogenesis is uncertain.

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251 DISEASES OF THE GALLBLADDER AND BILE DUCTS

Franz J Ingelfinger

Symptomatology The outstanding symptoms of disorders affecting the extrahepatic biliary system are pain and jaundice Very common but less specific symptoms are *fever* chills and a variety of *digestive disturbances*

Pain As is true of digestive viscera in general the major cause of pain in the biliary tract is an abrupt increase in intramural tension Thus any process which suddenly tenses the wall of the gallbladder or bile ducts—whether spasm or obstruction by tone—may precipitate biliary tract pain usually known as *biliary colic* To the patient biliary colic is severe and disabling a grinding pain that builds up rapidly persists maximally for 10 to 40 min tapers off gradually over hours and then terminates in a residual soreness lasting a day or more Although produced by smooth muscle and given the name *colic* biliary colic is a relatively steady pain without the extreme fluctuations characteristic of colic arising in the intestine Biliary colic originating in the hepatic or common duct is located high in the midepigastrium initially but spreads as the attack develops to the right and straight through the body to an area bounded by the vertebral column and the inferior angle of the right scapula If the gallbladder or cystic duct is the source of trouble colic is felt predominantly in the right epigastrium and tends to radiate along the costal margin to the right scapula Variants however do occur and in one out of ten cases pain extends principally to the left upper or right lower abdominal quadrant Biliary colic is not intensified by moving about—in fact the patient is often restless—but lifting the right arm or taking a deep breath may hurt presumably because of reflex spasm of upper abdominal and lower intercostal muscles

Gradual stenosis of the biliary passages as opposed to sudden obstruction is relatively painless Under such conditions an increase in intramural tension apparently is prevented by progressive atony of the biliary tract and diminished hepatic secretion

Biliary tract pain can also be caused by inflammation Slower in onset and duller in character this pain is also more persistent than biliary colic Because the inflammatory process usually irritates nearby parietal peritoneum pain of this type often becomes quite sharply localized in the right hypochondrium but patients with a markedly distended gallbladder or inflammatory mass projecting down to the level of the umbilicus place the maximum distress correspondingly lower

Jaundice Obstruction of the hepatic or common bile ducts leads to jaundice with regurgitation of free bilirubin and bile salts into the blood The rate at which jaundice appears and its degree depend upon the nature of the obstruction and the function of the gallbladder In gradual obstruction of the common duct as by neoplasm for example biliary congestion is initially cushioned by the storing and concentrating functions of the gallbladder which becomes greatly enlarged and filled with a thick and viscid concentrate of bile Jaundice usually does not become noticeable until considerable dilatation of both the extra and intrahepatic biliary tract has taken place In spite of the dilated bile channels within the liver however marked hepatic enlargement rarely occurs on the basis of bile stasis alone at first because of the safety valve function of the gallbladder and later because hepatic secretion is increasingly inhibited in the face of progressive biliary stasis With prolonged biliary obstruction indeed resorption of pigment from the stagnant bile takes place and may leave a clear and mucoid residue in the common duct

The situation is vastly different when the gallbladder is nonfunctioning or absent Under these conditions an acute obstruction of the common duct as by stone can produce slight icterus and choluria within hours and prolonged obstruction may lead to considerable enlargement of the liver particularly if biliary stasis is complicated by chronic infection Enlargement of the gallbladder is on the contrary unlikely since the nonfunctioning gallbladder usually has lost its elasticity and cannot take up bile

Complete occlusion of the cystic duct has little effect on a gallbladder permanently scarred by fibrosis but if the viscus is elastic it enlarges progressively to form a huge cystlike mass hydrops of the gallbladder The contents of a hydropic gallbladder gradually become colorless and occasionally calcium salts precipitate to form a turbid fluid known as *milk of calcium bile*

Fever and Chills These symptoms result from a combination of two factors biliary stasis and some mechanism permitting infection of the biliary passages Either condition alone is not enough For example patients with free regurgitation of chyme into the biliary radicles of the liver because of surgical anastomosis of hepatic duct to duodenum do not have fever or chills if the stoma is widely

patent Biliary stasis without infection as is characteristic of cancer in the head of the pancreas is likewise insufficient to cause fever and chills When biliary stasis occurs as a complication of gallstones however or when ulcerating cancers in the area of the ampulla of Vater allow bacteria to enter the common duct cholangitis develops and the patient is shaken by intermittent agues (Charcot's intermittent hepatic fever) The chills probably represent bouts of transient bacteremia

Disorders of the Gastrointestinal Tract Common manifestations of biliary tract disease include nausea vomiting belching epigastric bloating flatulence and constipation With severe biliary pain or inflammation intestinal distention and obstipation may be sufficiently marked to mimic obstruction of the gut Diarrhea is rare but may occur if an inflammatory cholecystic mass irritates the contiguous colon

If an obstruction of the biliary channels prevents bile from entering the intestine the digestion and absorption of fats is impaired and 10 to 40 per cent of the fat intake may be lost in the feces Fat soluble vitamins are similarly lost but the adult patient with biliary obstruction tolerates the loss of vitamins A D and E without serious consequences Decreased absorption of vitamin K however may rapidly induce hypoprothrombinemia

Impaired function of the gallbladder unlike obstruction of the common duct does not affect intestinal digestion or absorption and symptoms such as belching bloating and regurgitation are caused not by indigestion but by reflex disorders of gastrointestinal motility Thus the epigastric lump which distresses some patients after a fatty meal is not fat intolerance in the sense of impaired digestion of fat it is fat intolerance characterized by abnormal gastroduodenal motor mechanisms Since there are many extrabiliary causes for deranged gastroduodenal motility the symptoms of indigestion are not specific for gallbladder disease A patient with postcibal epigastric distress may have gallbladder disease or more likely a functional disorder unrelated to the biliary tract

Bleeding The question is often asked whether or not gallstones and their complications can cause bleeding into the gastrointestinal tract A few case reports exist of biliary tract bleeding caused by stones eroding into the hepatic artery or a minor vessel but as a general rule gallstones if not complicated by hypoprothrombinemia do not cause clinically significant blood loss

Biliary Tract Radiology

Radiopaque gallstones may be observed by plain films of the right upper abdomen To opacify various portions of the biliary system iodinated organic compounds excreted by the liver are used In routine cholecystography the compound is given by mouth Some 12 hr later the gallbladder contains sufficient dye to render it radiopaque provided that (1) gastrointestinal motility and absorption are normal (2) hepatic function is normal (3) the biliary channels are free of obstruction and (4) the gallbladder takes up concentrates and stores bile A gallbladder well filled with radiopaque dye indicates a normal viscus If radiolucent stones are present they are silhouetted against the contrast medium but small stones may at times be obscured by the very density of the dye This error may be avoided to a great extent by taking pictures with the patient standing or by taking successive pictures after evacuation of the gallbladder has been stimulated by a fatty meal (Fig 191)

Failure to visualize the gallbladder suggests an abnormal viscus provided the first three of the four conditions listed above are fulfilled At times even a normal gallbladder may fail to take up concentrate or store the dye This however happens only sporadically if the gallbladder fails to fill in each of two attempts at cholecystography the likelihood of gallstones is 90 per cent Poor concentration of the dye or increased or decreased rate of gallbladder evacuation in response to a fatty meal has little diagnostic significance Because of the enterohepatic circulation indeed a gallbladder may contain dye for many days following cholecystography

The dyes used for oral cholecystography are not sufficiently radiopaque to outline the biliary passages before concentration by the gallbladder The development of compounds (sodium iodipamide marketed as Biligrafin or Cholografin) which contain 65 per cent by weight of iodine and which are excreted by the liver (and in part by the kidney) within 5 to 50 min of their intravenous injection has permitted moderately satisfactory visualization of the larger biliary channels independent of gallbladder function Intravenous cholangiography is thus used to study patients whose gallbladders have been removed or are nonfunctioning because of disease A radiolucent stone in the common duct may at times be outlined by this procedure more often the partial obstruction produced by various choledochal lesions causes widening of the common duct (usual diameter less than 10 mm diameter over 15 mm definitely abnormal but magnification by x ray technique must be taken into account) and imparts a blunted dilated appearance to the intrahepatic radicles Like oral cholecystography intravenous cholangiography is unsuccessful in the face of hepatic disease or advanced biliary obstruction Failure to produce visualization with either procedure therefore has no diagnostic significance in a jaundiced patient On the other hand visualization of either the gallbladder or the bile ducts is at times possible in

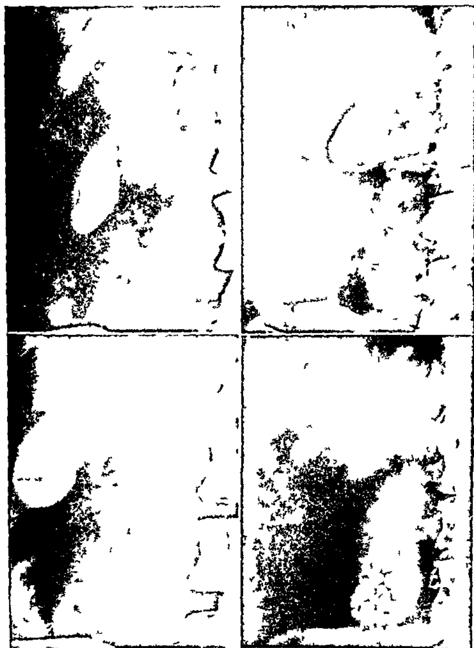


FIG 191 Results of cholecystography (*Upper left*) Normal gallbladder The concentrated radiopaque dye outlines the gallbladder and cystic hepatic and common ducts The dye appears in the ducts because this picture was taken after gallbladder evacuation had been stimulated by a fatty meal (*Upper right*) Cholelithiasis Nonopaque stones of varying sizes are shown as negative shadows within a gallbladder outlined by concentrated dye (*Lower left*) Cholelithiasis Numerous small stones are grouped in a layer near the bottom of the gallbladder This picture was taken with the patient standing Small stones such as these are dispersed when the patient is in a horizontal position and may be difficult to see (*Lower right*) Cholelithiasis Multiple radiopaque stones in a gallbladder with impaired concentrating ability

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las from the biliary tract to adjoining viscera and gallstone ileus In addition gallstones appear to predispose the gallbladder to cancer Although the likelihood of these complications is greatest in those who develop gallstones at an early age have many small stones or suffer repeatedly from biliary colic any gallstone including so called silent stones (i e asymptomatic stones discovered accidentally by x ray or at operation) must be regarded as a potential source of trouble

Patients with gallstones and one or more attacks of biliary colic should be treated by cholecystectomy there is no medical means of cure and the probability of further colics and worse complications is great Patients with stones who suffer merely from indigestion" also deserve to have the gallbladder removed but the complaints may not be alleviated completely because their relation to the gallstones may be merely coincidental Finally a middle aged woman with a "silent" stone faces the following choice

1 Do nothing In this case the chances are approximately even that she will develop symptoms warranting cholecystectomy later Furthermore because she faces the risks of serious complications surgical fatality and cancer of the gallbladder the chances are about six out of a hundred that the silent gallstone eventually will cause her death

2 Immediate elective cholecystectomy The mortality risk varies widely but it probably averages about 1 per cent throughout the country In addition there is a 0 5 per cent risk of a surgical accident leading to stricture of the common duct a crippling and potentially fatal complication

Most surgeons pointing to the 4 1 ratio of mortality risks between these alternatives recommend immediate cholecystectomy These statistics however give only a two dimensional picture The 1 5 per cent risk is immediate and threatens a woman just beyond middle age The 6 per cent risk is usually incurred when the patient is sixty five to seventy five years old an age when her life expectancy is threatened by many disorders In other words in terms of patient *years* nothing is gained by elective cholecystectomy and it appears reasonable to follow the patient with silent stone and to recommend surgery if and when the first biliary colic takes place

ACUTE CHOLECYSTITIS

Acute inflammation of the gallbladder is associated with gallstones nine times out of ten The part played by biliary calculi in precipitating acute cholecystitis is not clear but in some cases sudden occlusion of the cystic duct by a gallstone produces biliary stasis and thus promotes an eruptive growth of the few bacteria that indolently inhabit many calculous gallbladders In nearly half the cases however bile removed from an acutely inflamed gallbladder contains neither bacteria nor pus the evidence for a primary bacterial infection is not good To explain these cases it has been suggested that a stone in the cystic duct causes enough spasm and edema to compromise the nearby cystic artery with resultant ischemic damage to the gall bladder wall Acute cholecystitis has also been attributed to chemical irritants in the bile and in the case of noncalculous varieties to bacterial infection reaching the gallbladder by vascular or lymphatic routes

Symptoms Upper abdominal pain and fever are the outstanding symptoms The pain either may begin gradually or may explode with biliary colic thereafter it settles as a chronic but severe distress in the right upper abdomen Ten per cent of cases however usually comprising those of advanced age suffer relatively little pain Nearly all patients have fever not necessarily striking but often spiking to 101 F at least once in 24 hr Chills may precede the febrile peaks Nausea and vomiting are common but clinically perceptible jaundice appears in no more than 25 per cent of patients If icterus is severe an associated choledocholithiasis may be responsible milder and more transient bouts of jaundice can probably be ascribed to spasm edema or inflammation of the ducts draining the liver

Signs In addition to fever local signs ranging from slight muscular guarding and sensitivity on fist percussion to acute tenderness and boardlike spasm are found almost invariably in the right upper abdomen A tender vague mass comprising the swollen gallbladder and adherent omentum is palpable in roughly half the cases

Laboratory and X ray A quite consistent finding is polymorphonuclear leukocytosis ranging between 10 000 and 20 000 The results of other blood and urine tests are not remarkable except for the evidences of regurgitation jaundice in the icteric cases Bromsulphalein retention and increased serum alkaline phosphatase may be noted even in the absence of bilirubinemia X rays may show radiopaque gall stones and oral cholecystography usually reveals nonfilling of the gallbladder

Diagnosis The differential diagnosis includes coronary pleural and pulmonary diseases right sided heart failure perforated peptic ulcer pancreatitis mesenteric occlusion appendicitis acute salpingitis pyelitis intestinal obstruction and in jaundiced cases liver disease hemolytic crises and malignancy affecting the extrahepatic biliary system These conditions are differentiated rather easily from a typical case of acute cholecystitis particularly if clinical judgment can be supported by x rays electrocardiograms and appropriate examinations of blood and urine The atypical rela

patients with bilirubinemia up to 5 mg per 100 ml

Direct cholangiography consists of injecting an iodinated water or oil soluble medium into the common duct either at the time of surgery or subsequently while a t tube is maintained in the common duct In intact patients those experienced in the techniques can inject radiopaque substances into the biliary passages especially the gallbladder by means of a needle percutaneously inserted and guided once in the abdomen under peritoneoscopic control A more hazardous procedure is puncture of the liver with a percutaneously inserted needle that is advanced until bile is aspirated at this point the radiopaque dye is injected These last two techniques are indicated it is obvious only in jaundiced patients presenting difficult problems in differential diagnosis and not considered candidates for exploratory laparotomy

GALLSTONES

At the age of thirty a few women and a rare man have gallstones by the time they die 25 per cent of women and 10 per cent of men are so afflicted Why or how these stones form is still unknown In some instances as in the case of pigment (bilirubin) stones found in patients with chronic hemolytic anemia the high concentration of bilirubin in the bile may lead to the precipitation of pigment Similarly a postulated but unproved abnormality in the biliary excretion of lipids may explain why cholesterol stones are alleged to be more common in multiparous women in diabetic patients and in the obese Finally it is possible that changes in the wall of the gallbladder may disrupt the physicochemical equilibrium which keeps the biliary constituents in solution In hamsters a low fat diet deficient in vitamin A appears *to cause gallstone formation*

A patient may have one gallstone or he may have over 200 Multiple stones are usually small and faceted sometimes they occur in groups of several sizes as if produced in successive crops Larger stones commonly one to three in number tend to be round or elliptical Pure pigment or pure cholesterol stones are rare usually both substances make up a gallstone and approximately *50 per cent of stones contain sufficient calcium to* make them radiopaque

Symptoms and Signs Half the people with gallstones *have no biliary symptoms The other half* suffer distress ranging from mild postprandial belching and bloating to full blown attacks of biliary colic The episodes of colic occur intermittently each attack presumably representing the reaction of the biliary tract as a stone passes through the common duct or is wedged into the entrance of the cystic duct. As might be expected therefore stimulation of the gallbladder by a fatty meal may precipitate biliary colic but many an attack seizes the patient in the middle of the night without any obvious dietary reason At the *height of the colic* nausea vomiting and difficulty in taking a deep breath are frequent but not invariable complaints *Tenderness and spasm in the right upper abdomen* are present when pain is maximal but thereafter recede rapidly Residual sensitivity to fist percussion over the ribs may however persist for several days Between attacks the patient may feel in the best of health

Diagnosis Characteristic biliary colic typical in location and radiation is usually recognized without difficulty Though intense it is less disabling and prostrating than the pains of intestinal perforation mesenteric occlusion severe myocardial infarction or hemorrhagic pancreatitis Less severe forms of myocardial infarction or pancreatitis may however cause pain not easily distinguished from biliary colic As a rule biliary colic is briefer than the pain of pleurisy but lasts much longer than each fluctuating wave of intestinal colic Both biliary colic and peptic ulcer pain may occur during the night but biliary colic tends to strike in irregular and isolated attacks whereas the pain of severe peptic ulcer returns regularly night after night

Although biliary colic can often be recognized clinically roentgenologic examination (see Biliary Tract Radiology above) and on occasion duodenal drainage are indicated to establish the diagnosis Normal or technically unsatisfactory cholecystographic results in patients suffering from biliary colic should be supplemented by microscopic examination of bile obtained by duodenal drainage If cholesterol crystals are found in a nonicteric patient the chances are 80 per cent that gallstones are present if calcium bilirubinate 50 per cent *and if both substances are identified 95 per cent* It is thus possible to diagnose gallstones even in the absence of clear cut x ray findings provided that the patient has biliary colic and either (1) nonfilling of the gallbladder on two cholecystograms or (2) cholesterol crystals in the duodenal contents Similar findings by x ray and duodenal drainage in patients suffering from no more than indigestion" must be interpreted more cautiously but may be *considered as good if not indisputable evidence* of gallstones In a jaundiced case x ray techniques are often not helpful and duodenal drainage may *occasionally be misleading* because prolonged biliary stasis of whatever cause may lead to precipitation of cholesterol or more often of bilirubinate pigment

Course and Indications for Surgical Treatment The possible complications of gall tones are many acute and chronic cholecystitis choledocholithiasis cholangitis hepatic abscesses biliary cirrhosis fistu

the gallbladder and become arrested as they pass from gallbladder to duodenum but under some conditions biliary "mud" (precipitated bile pigment) and even larger concretions form in the hepatic and common ducts It is therefore possible that stones found in the common duct of a patient who previously had a cholecystectomy were deposited *de novo* but it is more likely that the stones were already in the biliary channels at the time of surgery but escaped detection

Symptoms and Signs Gallstones in the common duct cause biliary colic jaundice fever and chills but the pattern of these symptoms is variable A stone rapidly passed from gallbladder to duodenum may prostrate the patient with colic but the attack is brief afebrile and jaundice if present at all is light and evanescent Two out of every five patients with common duct stones removed at surgery have had no evidence of jaundice If stones pass more slowly or become lodged in the common duct biliary colic may be accompanied by chills and fever and is usually followed by a definite wave of jaundice with dark urine and light stools Nausea and vomiting are more prominent than with colic originating in the gallbladder Within 24 to 48 hr many attacks subside and the patient in spite of the continued presence of stones in the duct is quite well until movement of the stones spasm or inflammatory edema precipitates the next bout Though choledocholithiasis may thus be silent between attacks both extra and intrahepatic biliary passages are exposed to progressive dilatation and to smoldering infection by such organisms as *E cherichia coli Aerobacter aerogenes* and *Streptococcus fecalis*

The biliary obstruction caused by choledochal stones is not always transient Some attacks of colic are followed by persistent jaundice which may be constant or may fluctuate as the stones in the common duct shift position or as the inflammatory reaction waxes and wanes During this period deep discomfort in the right hypochondrium gradually replaces the initial colicky pains presumably because choledochal motility becomes fatigued in the face of continuing obstruction and inflammation In some patients with chronic distention and infection of the choledochal wall pain is never prominent and about 5 per cent of patients chronically jaundiced because of choledocholithiasis have what is called "painless jaundice" Fever and chills indicate that an ascending cholangitis is flourishing in the obstructed biliary passages and give warning that multiple hepatic abscesses or pylephlebitis may ensue if biliary stasis is unrelieved Other symptoms are anorexia meteorism constipation and pruritus

On physical examination tenderness and some muscular guarding are usually found in the right hypochondrium In chronically jaundiced cases the liver is enlarged 1 to 4 cm below the costal margin because of biliary stasis ascending cholangitis or both The skin is often excoriated and may show the purpuric manifestation of hypoprothrombinemia

Diagnosis When the whole clinical triad of biliary colic jaundice and spiking fever characterizes choledocholithiasis differential diagnosis from the other major causes of persistent jaundice i e liver disease and neoplastic biliary obstruction, is not difficult By contrast, jaundiced cases with little pain or fever are knotty diagnostic problems In these a past history of coliclike pain or a shaking chill points to choledocholithiasis Itching and failure to palpate the gallbladder should also characterize the jaundice of choledocholithiasis but often are relatively unreliable guides Splenomegaly argues against calculous biliary obstruction as does a history of colicless jaundice appearing after exposure to chlorpromazine or other drugs producing intrahepatic but cholestatic jaundice Intravenous cholangiography (see Biliary Tract Radiology above) has proved a great advance in establishing or excluding the diagnosis of common duct stones in patients who have biliary colic after cholecystectomy Other findings that suggest choledocholithiasis are leukocytosis bilirubinemia, bilirubinuria or increased amylase values in blood or urine samples taken within 3 to 12 hr of an attack of colic The diagnosis of choledocholithiasis is also supported by the discovery of abnormal biliary sediment on duodenal drainage and in jaundiced patients by a pattern of liver function and bile pigment tests indicative of a fluctuating regurgitation jaundice In the face of persistent cholangitis however flocculation tests may yield increasingly positive values

GALLSTONE ILEUS

Fistulous tracts formed by gallstones eroding through a chronically diseased gallbladder or common duct may enter any adjoining viscus but by far the most common route leads into the duodenum Large stones "hen s egg" size are most apt to be responsible and, strangely enough stones like this may erode into the gut without producing acute symptoms Hours to days later however an escaped gallstone sometimes enlarged by layers of inspissated intestinal material, may suddenly cause gallstone ileus i e it may acutely obstruct the distal ileum or very rarely the sigmoid Gallstone ileus accounts for only 1 to 2 per cent of all small bowel obstructions but should be suspected whenever an elderly woman who has had biliary symptoms for years suddenly experiences ileal obstruction The suspicion is changed to certainty if x rays show gas shadows outlining the biliary passages

tively painless case however may go undiagnosed To avoid this error any elderly patient with unexplained fever and leukocytosis should be suspected of biliary tract disease and extra care is warranted in examining the right upper abdomen for slight guarding minimal tenderness or a vague mass Sometimes a difficult diagnostic problem is presented by acute colonic obstruction which may closely simulate acute cholecystitis particularly if the responsible lesion is an ulcerated cancer near the hepatic flexure Although many cases of cholecystitis are nonicteric early and repeated examinations of blood and urine for even fleeting signs of jaundice are invaluable in the correct interpretation of acute abdominal disorders

Course Many attacks of acute cholecystitis subside within 1 to 4 days but in some 40 per cent of cases the process either does not abate or is progressive It is then that the danger of empyema gangrene or perforation of the gallbladder becomes acute Other threatening complications are cholangitis liver abscesses pancreatitis and pylephlebitis An occasional sequel of acute cholecystitis is erosion of the damaged gallbladder wall by a gallstone which thereafter may continue to lie outside the gallbladder but in 90 per cent of these cases escapes into the gastrointestinal tract by means of a fistula between the gallbladder and duodenum

CHRONIC CHOLECYSTITIS

Two types of chronic cholecystitis must be distinguished that which is clinically a bona fide entity and that which is not The bona fide variety presents the symptoms of acute cholecystitis in dilute and chronic form These include upper abdominal distress ranging from epigastric pressure to biliary colic indolent bouts of fever intermittent mild jaundice and various digestive complaints The right hypochondrium is often tender and almost invariably sensitive to fist percussion Cholecystography reveals nonfilling of the gallbladder In the vast majority of cases with these clinical and radiologic findings the pathologist finds a thick walled contracted gallbladder containing stones Rarely however no stones are found Under such circumstances the origin of the chronic inflammatory process is obscure Some cases may be the residuals of an acute hematogenous cholecystitis in other instances it is probable that stones were present initially but were then passed via the bile ducts or fistulous communications into the intestinal tract Bona fide chronic cholecystitis with the clinical and radiologic criteria here defined warrants cholecystectomy

The bogus variety of chronic cholecystitis is a straw man conveniently erected to explain functional digestive complaints and waiting to be felled by useless operation The patient usually has a large variety of digestive and systemic complaints but belching bloating and epigastric pressure after meals are predominant Fat intolerance in the sense that these symptoms are aggravated by a fatty meal is typical Tenderness may be elicited in many spots but objective abnormalities on physical examination are nil On cholecystography the gallbladder is outlined and shows no stones but the concentration of the dye or its evacuation in response to a fatty meal may not satisfy the radiologist

Patients with this clinical picture have been and are labeled as having chronic cholecystitis on the grounds that improper cholecystic function literally causes indigestion with deficient exposure of chyme to bile that variations in the concentration and evacuation of cholecystographic dyes provide a satisfactory index of gallbladder morphology and function and that chronic inflammatory and degenerative changes in the gallbladder wall furnish substantial evidence that the viscus causes clinical symptoms Actually patients with alleged chronic cholecystitis have no demonstrable digestive or absorptive defect the concentration and evacuation of gallbladder dyes are variable phenomena and in very few fields is correlation between structural change and clinical symptomatology so poor as in disorders of the gallbladder Many an oldster has pathologic evidence of advanced cholecystitis but never a biliary symptom and conversely the gallbladder affected by acute cholecystitis may reveal few of the pathologic changes usually expected of inflammatory disease The "strawberry gallbladder with its prominent mucosal and submucosal deposits of cholesterol is another entity which is striking pathologically but of nebulous significance clinically

Perhaps the best evidence that this variety of noncalculous chronic cholecystitis is not a real clinical entity is found in its treatment Those who treat the condition medically advise antispasmodics antacids laxatives rest and sedatives for the insomnia of which a majority of these patients complain measures that are usually marshaled to treat functional disorders of the alimentary tract Those who go further and remove an allegedly poorly functioning but stoneless gallbladder account for many of the failures of cholecystectomy Since the gallbladder is not the cause of the symptoms the patient can hardly be expected to benefit from its removal

CHOLEDOCHOLITHIASIS

Gallstones are found in the common duct in one out of every seven patients operated on for biliary tract symptoms Most of these stones originate in

ford relief but their effect is only temporary Methyltestosterone 25 mg daily has been used to control the itching of regurgitation jaundice Bile salts have been made unnecessary by the availability of fat soluble vitamins in water miscible form in fact since bile salts may increase pruritus their use is inadvisable

Dietotherapy From many points of view a diet low in fats (40 to 75 Gm per day) appears suitable for all types of biliary tract disorders For those with gallbladder stones one object of therapy is not to provoke movement of the stones into a position where they might produce symptoms Since the ingestion of fats is a stimulus for gallbladder motility the dietary restriction of fats appears rational, even though many colics and other complications of cholelithiasis have no clear cut relation to the size and composition of antecedent meals For those who suffer from belching epigastric pressure and bloating a diet relatively low in fats is also recommended partly on empirical grounds and partly because fats are particularly instrumental in affecting the gastroduodenal motor mechanisms that are responsible for many of the symptoms of "indigestion"

As far as the surgical treatment of biliary tract disorders is concerned the following principles pertain to most cases

1 If gallstones are to be removed the gallbladder is if possible removed as well Sometimes the condition of the patient or a technical difficulty precludes cholecystectomy and the surgeon must content himself with cholecystostomy to drain the gallbladder of stones fluid or pus The disadvantage of this procedure is that the gallbladder remains behind to serve as a further seat of inflammation and stone formation On the other hand removal of the gallbladder incurs no disability Except for some compensatory dilatation of the common duct the structure of the biliary channels remains unaltered and the digestion and absorption of fats are not impaired Cholecystectomy as far as the patient is concerned need not interfere with normal living and a normal diet

2 Every effort is made to free the common duct of calculi or crystals that might serve as a nucleus for further stones For this reason the common duct is explored not only in patients who have had obvious symptoms of choledocholithiasis but also in those who have a good probability of choledocholithiasis as indicated by a past history of jaundice the presence of many small stones in the gallbladder or the operative finding of choledochal dilatation The careful search for common duct stones often entails the meticulous probing and flushing of the duct After the common duct has been inspected and cleared of stones it is the usual practice to drain the duct by means of a t tube for several weeks During and after operation direct cholangiography is used to advantage to ensure that no stones remain

3 The acutely inflamed gallbladder is ideally removed at a time when technical difficulties are minimal but before perforation or gangrene develop Nearly all surgeons agree that these ideals are fulfilled if cholecystectomy is performed immediately in patients seen within 48 hr of the onset of symptoms but the management of patients seen later in the course of their disease is subject to sharp controversy Some operate as soon as the patient can be prepared for surgery Others prefer to wait 1 to 3 weeks until inflammatory reaction and tissue friability subside Surgeons in this group intervene only if increasing fever pain leukocytosis and general evidences of toxicity suggest impending necrosis or perforation of the gallbladder

4 In jaundiced patients with choledocholithiasis a waiting period is usually indicated before surgery is undertaken This gives the obstruction an opportunity to subside spontaneously or if jaundice persists time is available for carrying out the repeated tests often necessary to establish the correct diagnosis

BILIARY DYSKINESIA

Disorders of gastrointestinal motor function are generally accepted as adequate causes of abdominal pain The underlying mechanisms although not well understood are believed to consist of muscular spasms and lack of coordination between motor functions that normally are smoothly integrated Even more obscure are the nonorganic disorders that affect the extrahepatic biliary tract, but it is reasonable that pain may arise here as in the gut on the basis of spasm and incoordination.

The dynamics of the biliary tract are normally regulated by a coordinated inverse relationship between hepatic secretion cholecystic evacuation and choledochal tone on one hand and sphincteric mechanisms on the other This relationship however may be replaced under the influence of certain pharmacologic neurogenic or locally irritative stimuli by uncoordinated activity usually referred to as *biliary dyskinesia* The gallbladder for example may ineffectually attempt evacuation against a cystic duct tightly closed by spasm Alternatively a contracted sphincter of Oddi and duodenal musculature may oppose forces actively promoting bile flow In either case intraluminal pressure between the opposing forces is increased the wall of a hollow viscus is tensed and pain ensues

The archtype of biliary dyskinesia is provided by the spasmogenic effect of morphine on the duodenum and sphincter of Oddi To some extent this effect of opiates takes place in everyone but in

clear evidence of an abnormal communication between the biliary and enteric tracts

STRICTURE

One of the most distressing disorders of the biliary tract is chronic stricture of the hepatic or common duct Perhaps one tenth of such strictures are spontaneous in the sense that they appear mysteriously or are the direct results of choledocholithiasis In most cases however accidental injury of the common duct during gallbladder surgery is the cause Sometimes the surgeon recognizes that he has cut the duct and attempts repair more often he is unaware of the accident until the patient becomes jaundiced or develops an external biliary fistula some days after operation The exact incidence of such common duct injuries is unknown in experienced hands it is very rare but throughout the United States accidental injury of the common duct probably occurs in one out of every 200 cholecystectomies

Stricture whether spontaneous or surgically induced causes partial biliary obstruction usually complicated by chronic infection The biliary tree behind the stricture becomes progressively dilated its branches tortuous and damaged by varying degrees of cholangitis With virulent infection multiple hepatic abscesses may develop but the more common end result is biliary cirrhosis Clinically the patient exhibits a course slowly carrying him downhill over months to years Much of the time he suffers only from mild jaundice itching lassitude and digestive disorders but at irregular intervals he is suddenly seized by rigors and headache followed by sharp increases in jaundice These bouts probably are caused by transient exacerbations of the chronic cholangitis with bacteremia and increased biliary obstruction produced by the inflammatory reaction in the common duct

The only effective therapy is surgical correction of the partial obstruction sometimes with the creation of new biliary intestinal anastomoses This is surgery that requires a master but if repair is successful in the sense that bile flow is unimpeded not only is the patient symptomatically relieved but even advanced grades of biliary cirrhosis recede miraculously

TREATMENT OF GALLSTONES AND THEIR COMPLICATIONS

The only definitive treatment of a gallstone is its surgical removal Medical measures however are necessary to relieve pain to tide the patient over attacks and to prepare him for surgery For the relief of pain often the patient s first need meperidine (Demerol) is usually recommended on the premise that this narcotic analgesic unlike morphine *does not cause spasm of the sphincter of* Oddi Unfortunately this agent may not provide the necessary relief in which case an opiate may become mandatory The dramatic benefit which patients with biliary tract pain often obtain from morphine or one of its derivatives suggests that the harm done by morphine induced spasm of the sphincter of Oddi is of greater theoretical than real importance

During acute attacks of painful or inflammatory nature *nothing is given by mouth and meteorism* is forestalled by constant gastric suction Fluids and electrolytes are provided parenterally In patients with fever (i e those with acute cholecystitis choledocholithiasis with cholangitis stricture) antibiotics are indicated Although it is true that antibiotics will not appear in static bile dammed up behind an obstruction their dissemination by the blood tends to prevent the spread of infection and decreases the dangers of bacteremia Broad spectrum antibiotics are often used but the combination of parenteral penicillin (one to two million units per day) and streptomycin (1 0 to 2 0 Gm per day) appears preferable from the viewpoint of wide effectiveness and low toxicity

To prepare the patient for surgery deficiencies in fluid and electrolytes must be corrected transfusions must be given to debilitated or anemic patients and infection must be combated with antibiotics Parenteral infusions of glucose solution (100 Gm or more per day) are probably beneficial to the patient who cannot eat and ascorbic acid and factors of the vitamin B complex may help in a nonspecific way Of crucial importance is the parenteral administration of vitamin K preparations to any patient who is jaundiced or has had jaundice recently for the prothrombin resources of such patients may be unexpectedly low Formerly before preparation of this type was possible biliary tract surgery was sometimes followed by a mysterious syndrome called *liver death* an acutely fatal reaction *characterized by high fever jaundice* restless coma and renal failure This syndrome which probably comprised a number of disorders is rarely seen today presumably because biliary tract surgery is now aided by more accurate diagnosis preoperative correction of deficiencies better control of infection and improved anesthetic technique

When biliary obstruction is prolonged as in the case of certain strictures or neoplasms of the common duct the patient is given a low fat diet water soluble or water miscible preparations of vitamins K A D and E by mouth and sulfonamides or antibiotics as needed for the control of cholangitis One of the most distressing symptoms is apt to be itching which is only partially controlled by local applications Calcium gluconate injections may af

symptoms persist after operation for the obvious reason that removal of a noncalculous gallbladder falsely incriminated under the diagnosis of chronic cholecystitis cannot be expected to alter upper abdominal distress produced by an irritable colon or some other disorder of gastrointestinal function

CANCER OF THE GALLBLADDER

As far as the general population goes cancer of the gallbladder is a rare and unimportant disease For those who develop gallstones before the seventh decade however the picture is different for unless cholecystectomy is performed 3 per cent of this group will succumb to this cancer

The early symptoms of cholecystic cancer usually go unrecognized and are attributed to a benign biliary disorder particularly since two-thirds of the patients with this cancer give a history of biliary symptoms extending over years In any elderly patient with clinical or radiologic evidence of gallstones however the diagnosis may be suspected if pain becomes boring and persistent rather than acute and episodic and if weight loss occurs because of anorexia rather than because of voluntary restriction of food intake Moderate to severe jaundice usually stable or progressive is seen on admission in half the cases Because of associated infection of the biliary tract or because of tissue destruction within or by the tumor fever is common and chills not rare In 50 to 75 per cent of the cases a hard and tender mass is palpable in the right upper quadrant but this may be confused with inflammatory tumor of the gallbladder with biliary cirrhosis and with metastatic nodules in the liver

Cancer of the gallbladder usually spreads by direct invasion of the liver and the vital structures of the hepatic porta Its successful surgical extirpation consequently is well nigh impossible and 5 year cures are reportable rarities

CANCER OF THE BILE DUCTS

Adenocarcinoma may grow in any portion of the bile ducts occasionally in the right or left hepatic duct sometimes in the common duct close to the ampulla of Vater but most frequently near the junction of the hepatic and cystic ducts It is not a common cancer In men who appear to be more frequently affected than women it occurs about one fifth as often as pancreatic cancer The clinical manifestations are similar to those of cancer in the head of the pancreas but may be modified by superimposed infection or by elimination of cholecystic function Thus cancers situated at or above the junction of the cystic and hepatic ducts produce hepatomegaly rather than enlargement of the gallbladder (Table 128 Chap 249) Although resection of early cancer in the distal common duct is possible the prognosis is usually hopeless as the growth spreads and secondary infection as well as persistent biliary obstruction impair hepatic function With increased attempts to examine the duodenal contents for exfoliated neoplastic cells and with additional experience in newer methods of cholangiography earlier diagnosis of some of these growths may be possible

UNUSUAL CONDITIONS

Congenital abnormalities of the gallbladder include complete absence of the viscus anomalous structure such as double gallbladder and unusual position within the liver or the anterior abdominal wall The bile ducts are also subject to numerous congenital defects among which atresia and cystic dilatation are the most prominent

Cholecystitis due to *Salmonella* is rare where salmonellae infections are controlled but formerly typhoidal infection of the gallbladder was responsible for many typhoid carriers Very infrequent causes of biliary tract infection are tuberculosis syphilis actinomycosis and septic emboli The characteristic lesions of periarteritis nodosa are sometimes exceptionally prominent in the walls of the gallbladder

The biliary tract may be infested by *ascarids liver flukes* and *Echinococcus cysts* These parasites may cause biliary obstruction with cholangitis and jaundice A parasite found in the United States in about 0 5 per cent of patients examined by duodenal drainage is *Giardia lamblia* but the pathogenicity of this organism is questionable

With improved cholecystography *small polypoid masses* are discovered not infrequently in the gallbladder but their clinical significance is controversial Many of these polyps are merely mucosal prominences containing localized cholesterol deposits much more rarely true adenomatous growths occur In either case the lesion cannot be held responsible for symptoms That the adenomatous polyps progress to cancer is a vehement but unproved assertion used by those who insist on cholecystectomy whenever a polyp is discovered radiologically in the gallbladder

Traumatic Rupture of the Gallbladder with bile peritonitis occasionally is a serious complication of abdominal injuries

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hypersensitive patients opiates induce intense nausea vomiting and a violent contraction of the duodenum and sphincter of Oddi with biliary colic A similar though less well documented dyskinetic mechanism may account for the biliary type of pain that sometimes occurs during migrainous attacks for neurogenic nausea is usually accompanied by considerable duodenal spasm Finally it may be postulated that biliary dyskinesia is caused by cholinergic or adrenergic imbalance by reflexes from other organs and by locally irritative foci such as cystic duct remnants following cholecystectomy or the scars of spontaneous or operative injury In continental Europe and South America biliary tract motor abnormalities are analyzed much more minutely and a host of syndromes have been proposed on the basis of hypotonia hypertonia and atony of various parts of the tract The evidence for these syndromes is unconvincing

Symptoms Signs Diagnosis and Treatment Clinically the pain tenderness nausea and vomiting of biliary dyskinesia closely mimic organic disease of the gallbladder and bile ducts but jaundice fever chills and leukocytosis do not occur For purposes of management the syndrome may be divided arbitrarily but conveniently into three types

In the first type biliary dyskinesia appears as part of a more general syndrome in which various autonomic phenomena may be prominent The patient a woman nine times out of ten usually has had a stoneless gallbladder removed Headache giddiness scotomas nausea or some other aura may *precede* the biliary colic (in organic biliary tract disease pain is usually the first symptom) sweating and pallor may accompany it and loose bowel movements may follow A careful history may reveal that the attack has been precipitated by the ingestion of a minute quantity of opiate as may be found in many analgesics or cough medicines If this clinical picture is accompanied by completely negative laboratory and radiologic studies particularly a normal intravenous cholangiogram the treatment is medical In essence it consists of (1) reassurance (2) avoidance of opiates in all forms and (3) a combination (admittedly shot gun in character) of sedatives and antispasmodics to be taken at the very first sign of the attack e g salicylates anticholinergics and barbiturates or tranquilizers are given in combination and maximal oral doses in an effort to abort the attack and put the patient to sleep Since this type of dyskinesia resembles migrainous episodes in some respects ergotamine or Cafergot 3 to 5 tablets by mouth may be tried Once the attack is well on its way the physician may be forced to give meperidine subcutaneously

The patient with the second type of biliary dyskinesia has had a cholecystectomy for gallstones but biliary colic has persisted or returned and no studies made *provide any explanation* Unlike the colic in type I the colics in type II are not associated with other phenomena The attack *may be* treated with the combination of salicylates anticholinergics and sedatives or nitrites may be used in an effort to relieve muscular spasm If such measures fail however surgical exploration appears justified since an organic cause for the pain may exist in this type of case in spite of the negative *findings* If no obvious cause is found at operation management is difficult if a t tube is inserted and the patient is maintained on constant common duct drainage no attacks develop as long as the tube is in place Once the tube is removed the colics return whether or not procedures such as dilatation or cutting of the *sphincter of Oddi have been* attempted

Type III is the rarest The patient usually female has a normally functioning gallbladder but intermittently its emptying appears to be prevented perhaps by cystic duct spasm Treatment is medical a low fat diet with the salicylate anticholinergic sedative combination being used for the intermittent attacks

POSTCHOLECYSTECTOMY SYNDROME

The term *postcholecystectomy syndrome* is often used in referring to real or alleged biliary symptoms which persist after cholecystectomy but which cannot be explained on the basis of residual or new biliary calculi It thus serves as a scrap basket term which comprises a number of conditions

1 Organic abnormalities of the bile ducts such as stricture fibrosis of the sphincter of Oddi cystic duct stump and tumors of nerve tissue A cystic stump remaining after cholecystectomy has become a more important entity since the advent of intravenous cholangiography Such stumps may enlarge and may serve as a site for new gallstone formation Some surgeons hold cystic stumps responsible for symptoms whether or not additional disorders are present but this view appears untenable because uncomplicated cystic duct stumps are seen as often in normal postcholecystectomy patients as in those complaining of symptoms

2 Chronic relapsing pancreatitis

3 Biliary dyskinesia The operative record in most of these cases shows that no stones were found at cholecystectomy and it may be assumed that biliary dyskinesia accounts for both pre and postoperative symptoms In a few cases however biliary dyskinesia appears to affect patients who underwent cholecystectomy because of the sound indication of cholelithiasis

4 Functional gastrointestinal disorders In this the largest group of postcholecystectomy syndromes

The taking of the history and the physical examination then are the primary and fundamental methods in diagnosis Where there is disagreement as to diagnosis it will often be discovered that the source of the difficulty is an uncertainty as to the significant items in the history or physical examination Repeated examination may be necessary in order to establish them beyond doubt This is why it is said that the second examination is the most helpful diagnostic method in a difficult case

Different disease processes may cause identical symptoms which is understandable from the fact that several diseases may involve the same parts of the nervous system For example a spastic paraplegia may result from spinal cord tumor syphilitic meningomyelitis or multiple sclerosis Or one disease may cause several different symptoms Despite the almost infinite number of possible combinations of symptoms and signs a few occur with greater frequency than others and these can be *recognized as symptom complexes or syndromes* The experienced clinical worker acquires the habit of attempting to categorize every clinical case by placing it under one or another syndrome In doing so he more or less determines the anatomic basis of the illness in question and then proceeds to a search for etiologic factors

The final diagnosis must state the locality of the disease as well as its nature and to be complete should express the degree of functional impairment as well Anatomic diagnosis has precedence over etiologic diagnosis To seek the cause of a disease without first ascertaining the part or parts of the nervous system which are affected would be analogous in internal medicine to attempting etiologic diagnosis without knowing whether the disease involved the lungs stomach or kidneys

The study of neurology should always proceed from the general to the specific The student must learn the identity and differential diagnosis of the common syndromes before the details of individual diseases It should be kept clearly in mind however that syndromes are not diseases but rather abstractions set up by clinical workers in order to facilitate the diagnosis of disease The inherent danger in the method is that it may inculcate a rigidity of thinking and keep one from conceiving of diseases in new relationships

TAKING THE HISTORY

Skill in taking a clear meaningful history of an illness *is the mark of an able clinician In fact this* faculty more than any other distinguishes the competent from the incompetent clinical worker The following three points about history taking in neurology deserve comment

1 Special care must be exercised to avoid suggesting to the patient the symptoms that one seeks The clinical interview is a bipersonal engagement and the conduct of the examiner has a great influence on the patient Psychiatrists have talked and written about this so much that the repetition may seem tedious but it is evident that many of the conflicting histories presented on ward rounds can be traced to leading questions that have suggested to the patient the symptoms that the examiner expects to find or to an unconscious distortion of the patient s story Errors and inconsistencies in recording the history are as often the fault of the physician as of the patient Here the practice of making bedside notes is particularly to be recommended Considerable experience may be necessary to keep a suggestible and highly circumstantial patient on the subject of his illness and of course discreet questions are always necessary to draw out certain important points

2 The mode of onset and the course of the illness *are of paramount importance Often the nature* of the disease process can be decided by these facts alone One must know how each symptom began and progressed from the onset of the illness to the present If the patient cannot supply this information it may be necessary to judge the course of the symptoms by what he was able to do at different times i e how far he could walk whether he could carry on his work etc or by changes in the clinical findings between successive examinations Following a case and allowing time for a disease to evolve a method relied upon by all astute physicians takes advantage of the latter procedure

3 Since neurologic diseases often derange the patient s mind it is necessary in every case to decide during the interview by assessment of the mental status and the circumstances under which symptoms occurred whether or not he is competent to give the story of his own illness If not the history must be obtained from an outside source such as a relative friend or employer The nature *of certain illnesses such as a convulsion obviously* precludes the patient s knowledge of all the details of that part of his illness In general students and some physicians as well tend to be careless in the estimation of the mental capacities of their patients An attempt is sometimes made to take a history from a patient who is feebleminded or so confused that he has no idea why he is in a doctor s office or a hospital or from one who could not possibly have been aware of the details of the illness

THE NEUROLOGIC EXAMINATION

The neurologic examination begins always with the history The manner in which the patient tells the story of his illness may betray lack of coherence

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Section 7 The Nervous System

252 APPROACH TO THE PATIENT WHO HAS A NEUROLOGIC PROBLEM

Raymond D Adams

Neurology is often regarded as one of the most difficult and exacting specialties of medicine The student coming to the neurology clinic for the first time is already somewhat intimidated by the complexity of the nervous system through his brief contact with neuroanatomy neurophysiology and neuropathology and often has a defeatist attitude The ritual he then witnesses of putting the patient through a series of maneuvers designed to evoke certain mysterious signs named after famous neurologists or called by unpronounceable terms does not reassure him In fact it often appears to conceal the very intellectual processes by which neurologic diagnosis is attained Moreover he has no aptitude for the many special tests which are used such as the lumbar puncture and cerebrospinal fluid examination and the electroencephalographic pneumoencephalographic and arteriographic examinations and does not know how to interpret the results of such tests when they are given him Neurologic textbooks only confirm his fears as he reads the details of the countless rare diseases of the nervous system

THE CLINICAL METHOD

The writer believes that many of the students difficulties with neurology may be overcome by proper instruction in the basic principles of clinical medicine First and foremost he must know and acquire facility in the use of the *clinical method* Without a clear comprehension of this method he is virtually as helpless with a new problem as would be the botanist or chemist who attempted to do research without having learned the scientific method

The importance of the clinical method stands *out more clearly in the study of neurologic diseases* than in certain other fields of medicine but the following remarks nevertheless have universal application The solution of any clinical problem is reached by a series of inferences and deductions each an attempt to explain an item in the history of an illness or a physical finding Diagnosis is the mental act of selecting the one explanation most compatible with all the facts of clinical observation Probably no two minds function exactly alike in this process and indeed one physician may not reason the same way on two different clinical problems Yet an analysis of the clinical method used will show that it generally consists of an orderly series of steps as follows

1 The essential clinical data are secured by history and physical examination

2 Those clinical data which are considered relevant to the current problem are interpreted and *translated in terms* of anatomy and physiology Certain complexes of symptoms and signs are recognized as having a meaningful relationship This may be called *syndromic diagnosis*

3 These data enable the physician to determine *the anatomic localization that best explains these* findings This may be called the *anatomic diagnosis*

4 The course of the illness the associated medical findings and the accessory laboratory data are then evaluated

5 And finally the *etiologic diagnosis* is educed from these data and from the location of the disease process

The elicitation of accurate and reliable data concerning the disordered functioning of the nervous system is the first step in diagnosis If these data are incorrect the diagnosis will surely be erroneous

Attention speed of response ability to give relevant answers to simple questions and in general the capacity for sustained mental effort all lend themselves to straightforward observation Useful bedside tests of attention memory and clarity of thought are the repetition of a series of digits in forward or reverse order serial subtraction of 7s from 100 the recall of the names of three objects after an interval of 3 min and the solution of simple problems and riddles Other tests can be devised for the same purpose Often the examiner can obtain a better idea of the clearness of the patient s sensorium and the soundness of his intellect by giving him a few tests and noting the manner in which he deals with them than by relying on a crude score of a formal intelligence or achievement test (see Chap 36)

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The remainder of the neurologic examination should be performed as part of the general physical examination and not as a special procedure to be done later if indicated It should always be carried out in an orderly systematic manner proceeding from the examination of the cranial nerves to the upper extremities trunk and lower extremities in order to avoid omissions The cranial nerves can be tested along with the examination of the eyes ears nose and throat The arms should be examined after the cervical structures and before the heart and lungs and the legs before the pelvic and rectal examination Gait and station should be observed at some time during the procedure usually before or after the rest of the examination

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The Comatose Patient Although subject to ob vious limitations examination of the stuporous or comatose patient may yield considerable informa tion concerning the function of the nervous system The special techniques involved have been pre sented in Chap 33 Coma and Related Disturbances of Consciousness

The demonstration of signs of focal brain disease or of meningeal irritation is of aid in the differential diagnosis of the diseases which cause coma As al ready pointed out three syndromes are discernible

1 Coma without meningitis (or changes in cerebrospinal fluid) or signs of focal lesions in one or the other hemisphere or brain stem This is usually due to drug intoxication or a metabolic dis ease such as diabetic acidosis uremia liver coma *hypoglycemia* Addison s disease etc

2 Coma with meningeal irritation and changes in cerebrospinal fluid but without signs of focal lesions of the brain Meningitis or subarachnoid hemorrhage is the usual cause

3 Coma with signs of a focal lesion of the brain with or without signs of meningeal irritation or changes in the cerebrospinal fluid This is usually due to a brain hemorrhage infarction tumor abscess encephalitis or epidural or subdural hema toma In any one of these syndromes a convulsion may cause a serious transitory derangement of con sciousness that confuses the clinical picture

The Psychiatric Patient One is compelled in the examination of psychiatric cases to rely less on the cooperation of the patient and to be unusually critical of his statements and opinions The de pressed patient for example may declare that his limbs are weak or useless when actually there is little or no diminution in muscular power or the psychopathic patient may feign paralysis The op posite is sometimes true—that the most psychotic patient may make accurate observations of his own *symptoms only to have them ignored because the* attending physician has been in the habit of disre garding his complaints

If the patient will speak and cooperate to the slightest degree much may be learned as to the functional integrity of different parts of the nervous system Aphasia can in nearly every instance be diagnosed by the manner in which the patient uses words in phrases and sentences or responds to spoken or written commands Often it is possible to determine whether there are hallucinations de fective memory or other symptoms of recognizable brain disease merely by watching and *listening to* the patient The visual fields can often be tested with fair accuracy by observing the patient s re sponse to a moving stimulus or threat in all four quadrants of the fields The tests of cranial nerve motor and reflex function in the legs outlined above for the examination of the stuporous and comatose patient can be carried out even better if minimal cooperation is obtained from the patient It must be remembered however that the neurologic ex amination is never complete unless the patient will speak and carry out the usual tests On numerous occasions mute patients judged to be schizophrenic have had some widespread cerebral disease such as hypoxic or hypoglycemic encephalopathy a brain tumor a vascular lesion or extensive de myelinative lesions

Infants and Small Children At an early age before a child has learned to speak or carry out spoken commands neurologic disease manifests it self almost exclusively as a disturbance of sensori motor reactions Many parts of the neurologic ex amination which are of value in testing nervous

function in adults are of little use in infants For example the tendon and plantar reflexes are seldom of much help The examination of the optic fundi rarely is of value except in amaurotic familial idiocy toxoplasmosis or tuberous sclerosis Sensory tests except response to painful stimulation are not worthwhile More can be learned by merely sitting at the bedside for a few minutes and observing the activity of the patient than by attempting special tests Within a few minutes the average infant who is awake will move every muscle in the body Rigidity or spasticity of the limbs or paralysis of a muscle or group of muscles is easily discovered by merely observing these motor performances and by manipulating the limbs

The neurologic examination of the infant and small child should always begin with careful inspection of the head and palpation of the anterior fontanel Peculiarities in the shape and size of the skull are often found with brain disease The head is unnaturally small in many cases of amentia with gross brain lesions and unilaterally small with hemiatrophy of the brain Premature closure of sutures which accounts for odd shapes of the skull is frequently associated with brain disease and developmental retardation And of course enlargement of the head may occur with hydrocephalus chronic subdural hematoma and rarely macrocephaly Retarded children who remain in one position because of a postural abnormality due to nervous disease may show flattening of the skull on one side A bony defect a tuft of hair or a peculiarity in the skin over neck and spine permit diagnosis of a cranium bifidum or spina bifida (see Chap 253)

Visual activity assumes particular importance after the first 2 or 3 weeks of life Conjugate movements of the eyes in fixating and following a visual stimulus develop early The coordination of hand and eye and alertness to a moving stimulus introduced in various parts of the visual field are normally acquired in the first 1 to 3 months Retardation in these activities suggests a specific visual defect or a general disturbance in nervous development Attentiveness and response to sounds also constitute a good test of sensorimotor organization and of adaptive behavior

The organization of motor activity in head control in grasping and reaching for objects in sitting crawling standing walking and vocalizing are reliable indices of the functional activity of the nervous system Social behavior may later be used in the same way as a sign of nervous organization These motor skills and adaptive and social behavior develop in an orderly sequence a timetable has been established by Gesell and other workers The developmental quotient a figure arrived at by comparing chronologic age with developmental age expresses the degree to which motor development is retarded Unless conditioned by psychologic factors a significant degree of retardation of development signifies a disease of the brain which may prove as time passes to be regressive stationary or progressive The subsequent course of the illness should distinguish these three classes of disease A progressive brain disease not only interferes with the normal processes of maturation but may cause an actual regression in behavior

Neurologic diseases in infancy may be extensive without causing obvious focal neurologic signs and it must be assumed that the functions of a large part of the cerebrum and basal ganglions are in abeyance during the early months of life Cerebellar ataxia and motor and sensory paralysis from cerebral lesions may not be recognizable at this time In fact seizures general motor inactivity lack of startle reaction opisthotonos and abnormal postures poor regulation of breathing and inability to suckle are the only dependable neurologic signs during the first days and weeks of life

The author has found the methods of examination outlined by Gesell and Amatruda and by Andre Thomas to be of far greater value in infants than those customarily employed by neurologists However the limitations of a clinical method that depends largely on assessment of the strictly motor aspects of behavior are obvious Experience in pediatric neurology dictates caution in prognosticating the potential mental capacities of an infant until there is a sufficient degree of maturation to permit the testing of the more specific sensorial and intellectual faculties of the mind

IMPORTANCE OF A WORKING KNOWLEDGE OF NEUROANATOMY AND NEUROPHYSIOLOGY

Once the technique of obtaining reliable clinical data is mastered the student may find himself handicapped in the interpretation of the findings by a lack of facility in neuroanatomy and neurophysiology These are highly complex subjects and to acquire a practical working knowledge of them is time consuming Fortunately these subjects are taught well in most schools and those principles which are immediately applicable to the clinical neurologic problem are not too difficult.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the cause of a clinical syndrome requires knowledge of an entirely different order One must be conversant with the clinical details and the course and natural history of the more common disease entities Many of these facts are simple and well known and can be found in any standard textbook on neurology For instance the distinguishing characteristic of vascular

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3 Coma with signs of a focal lesion of the brain with or without signs of meningeal irritation or changes in the cerebrospinal fluid This is usually due to a brain hemorrhage infarction tumor abscess encephalitis or epidural or subdural hema toma In any one of these syndromes a convulsion may cause a serious transitory derangement of con sciousness that confuses the clinical picture

The Psychiatric Patient One is compelled in the examination of psychiatric cases to rely less on the cooperation of the patient and to be unusually critical of his statements and opinions The de pressed patient for example may declare that his limbs are weak or useless when actually there is little or no diminution in muscular power or the psychopathic patient may feign paralysis The op posite is sometimes true—that the most psychotic patient may make accurate observations of his own symptoms only to have them ignored because the attending physician has been in the habit of disre garding his complaints

If the patient will speak and cooperate to the slightest degree much may be learned as to the functional integrity of different parts of the nervous system Aphasia can in nearly every instance be diagnosed by the manner in which the patient uses words in phrases and sentences or responds to spoken or written commands Often it is possible to determine whether there are hallucinations de fective memory or other symptoms of recognizable brain disease merely by watching and listening to the patient The visual fields can often be tested with fair accuracy by observing the patient s re sponse to a moving stimulus or threat in all four quadrants of the fields The tests of cranial nerve motor and reflex function in the legs outlined above for the examination of the stuporous and comatose patient can be carried out even better if minimal cooperation is obtained from the patient It must be remembered however that the neurologic ex amination is never complete unless the patient will speak and carry out the usual tests On numerous occasions mute patients judged to be schizophrenic have had some widespread cerebral disease such as hypoxic or hypoglycemic encephalopathy a brain tumor a vascular lesion or extensive de myelinative lesions

Infants and Small Children At an early age before a child has learned to speak or carry out spoken commands neurologic disease manifests it self almost exclusively as a disturbance of sensori motor reactions Many parts of the neurologic ex amination which are of value in testing nervous

Some of these conditions are manifest at birth others may be recognized only in late infancy and early childhood after some degree of maturation is attained Together these diseases comprise a large segment of pediatric neurology and to discuss them fully it would be necessary to touch upon the entire field of nervous disease in infancy and childhood However in a textbook of medicine limitations of space prevent the presentation of pediatric disease and for this reason only those conditions which permit long survival and are likely to come to the attention of the internist and general physician are considered

MAJOR PROBLEMS OF PEDIATRIC NEUROLOGY

The diseases included in this chapter differ from most of those acquired in late childhood adolescence and adult life in that they are likely to cause deformity of the skull spine and limbs delayed or abnormal motor and speech development or mental retardation The corollary of this axiom is that when any one of these abnormalities is observed in the adult there is a strong probability of a disease of the nervous system that had its onset before birth or during infancy or early childhood Understanding fully the significance of these three types of abnormality will enable the student or physician to deal effectively with the majority of patients who suffer from developmental abnormalities For this reason this chapter is devoted to an exposition of these topics In addition certain seizure problems peculiar to the pediatric age group deserve special consideration here

Malformations of the Cranium Spine and Limbs

A congenital abnormality may be defined as a structural defect in some tissue or organ of the body which is present at birth It may be gross or microscopic on the surface of the body or within it familial or sporadic hereditary or nonhereditary single or multiple (Warkany)

Estimates as to the incidence of congenital abnormalities of the nervous system vary substantially depending upon the definition adopted by the reporter and the time in life when the survey was made Malpas found a congenital malformation of the nervous system in approximately 1 per cent of 13 000 births and McIntosh and his associates give a figure of 1 3 per cent of total births 7 2 per cent of stillbirths 6 1 per cent of infants dying in the first days of life and 1 1 per cent of live births Malformations of the central nervous system are of importance in stillbirth and infantile mortality They cause 76 per cent of all fetal deaths prior to birth and 69 per cent of deaths in the first year of life according to Record and McKeown As was pointed out by Murphy the nervous system is involved in 60 per cent of all patients with a congenital malformation

General understanding of these malformations has been advanced by experimental teratology a branch of biology that seeks the causes of abnormalities of structural development In the progeny of animals possessing certain abnormal genes developmental abnormalities can be predicted in ratios that agree with established genetic laws Equally predictable results have been obtained by subjecting the embryo or fetus under controlled conditions to certain environmental stresses X ray hypoxia deficient diet viral infections and toxic substances have been shown to induce a variety of defects in the central nervous system depending on the stage of embryogenesis at which the noxious agent is applied to the pregnant animal These genetically and environmentally determined malformations serve as experimental models which can be investigated to great advantage

In human beings both genetic and environmental factors have been established in the production of congenital defects Neurofibromatosis (von Recklinghausen) encephalotrigeminal syndrome (Sturge Weber Dimitri) cerebelloretinal syndrome (Lindau and von Hippel) craniofacial dysostosis (Crouzon) optic atrophy (Leber) and craniostenosis with syndactylism (Apert) have a dominant pattern of inheritance the lipid storage diseases (Tay Sachs) and gargoylism (Hurler) phenylketonuria hepatolenticular degeneration (Wilson) Hallevorden Spatz disease and galactosemia are examples of recessive heredity Specific enzymes are found to be lacking in some of these diseases and are suspected of being absent in others Examples of malformations due to the action of a noxious agent during human development are less numerous Roentgen radiation during the first trimester of pregnancy has been observed to produce a combined cerebral cerebellar defect with mental retardation and ataxia Maternal infection with German measles (rubella) during the first trimester of pregnancy may result in mental defect deafness cataracts and heart disease in the newborn Toxoplasmosis and syphilis may damage the fetal nervous system in the latter half of the period of intrauterine life Isoimmunization by Rh and ABO blood factors may affect the nervous system during the first days of postnatal life leaving in its wake a permanent mental defect choreoathetosis and deafness

Abnormalities of the Head

Alterations in the size and shape of the head when observed in the adult can usually be traced to infancy At least three separate factors are operative (1) the growth thrust of the developing brain and the intracranial pressure (2) the time at which

disease of the brain is its sudden onset and if death does not occur the improvement in the patient s neurologic status Similarly insidious onset and slow progression often punctuated by convulsions are typical of brain tumor

The findings in the general medical examination are of importance the fallacy of studying nervous symptoms and disregarding the general medical findings must be obvious To illustrate low grade fever anemia heart murmur and splenomegaly indicate that in a case of unexplained apoplexy subacute bacterial endocarditis with embolic occlusion of a brain artery is the most likely cause Pleocytosis in the cerebrospinal fluid with elevated protein abnormal gold sol and a positive Wassermann test reaction establish a syphilitic etiology in a case with symptoms of apoplexy a progressive dementia or blindness

The anatomic diagnosis may suggest the etiology of a disease Thus when a unilateral Horner s syndrome cerebellar ataxia paralysis of a vocal cord and analgesia of the face are combined with loss of pain and temperature sensation in the opposite arm trunk and leg an occlusion of the posterior inferior cerebellar artery is suggested because all the involved structures lie within the territory of this artery In a sense the anatomic diagnosis determines and limits the possible disease entities If the signs point to disease of the peripheral nerves it is not necessary to consider the causes of disease of the spinal cord Some signs themselves are almost specific e g Argyll Robertson pupils for neurosyphilis or oculogyric crises for postencephalitic parkinsonism

If one adheres faithfully to the method of making these clinical observations and to the interpretations and methods of reasoning neurologic diagnosis becomes relatively simple In nearly every case it will be possible to reach an anatomic diagnosis The etiology of the disease may prove more elusive Even the most experienced neurologist is unable to ascertain the cause of many neurologic syndromes

THE PURPOSE OF THE CLINICAL METHOD OF NEUROLOGY

Finally a word about the main purposes of the clinical method of neurology Actually diagnosis accomplishes two purposes First it enables the physician to decide on the proper method of treating the ailing patient and second it serves as an essential method in the scientific study of disease by permitting the identification and segregation of clinical phenomena The medical profession is primarily concerned with the prevention and cure of illness and all our knowledge is applied to this well defined end The practical physician applies himself to the diagnosis of diseases for which he has an effective treatment Each of the treatable causes of a given syndrome must be carefully considered and excluded by clinical and laboratory methods In the study of a case of disease of the spinal cord one must take special care to diagnose a tumor subacute combined degeneration spinal syphilis or epidural abscess for these are the treatable spinal cord diseases Failure to recognize amyotrophic lateral sclerosis is a less serious error as far as the patient is concerned The failure to diagnose one case of chronic subdural hematoma is more serious than the incorrect diagnosis of several cases of brain tumor

One cannot agree with those who hold that neurologic diagnosis is merely an intellectual pastime It is true that means are available for treating only a few of the many diseases known to affect the nervous system But there is no doubt that the first step in the scientific study of a disease process is the identification of it in the living patient Until this is achieved it is impossible to apply adequately the master method of controlled experiment The clinical method of neurology thus serves both the physician in the practical diagnosis and treatment of a patient and the clinical scientist who seeks the ultimate cause of disease

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253 DEVELOPMENTAL ABNORMALITIES OF THE NERVOUS SYSTEM

Philip R Dodge and Raymond D Adams

The human nervous system is subject to a variety of developmental abnormalities which may be traced to genetic faults or to diseases acquired in utero at birth or during the early years of life

abnormality an accompaniment of an Arnold Chiari *malformation* or of neurofibromatosis or the result of a chronic meningoependymal *inflammation*

3 *Atresia of the foramens of Luschka and Magendie* (*Dandy Walker syndrome*) with obstructive hydrocephalus and enlargement of the posterior fossa Here the basal foramens fail to form or are sealed off and the cerebrospinal fluid cannot enter the subarachnoid space

4 *Chronic meningitis* with communicating or obstructive hydrocephalus This is due to obliteration of the subarachnoid space over the brain stem and/or obstruction of the foramens of Luschka and Magendie The meningitis may be due to syphilis toxoplasmosis or a chronic pyogenic or other in*fection*

5 *A tumor* of the fourth ventricle (medulloblastoma ependymoma or teratoma) of the third ventricle (craniopharyngioma) or of the pineal body (teratoma) may cause obstructive hydrocephalus (see Chap 73)

6 Other conditions such as hypertrophy of the choroid plexuses and achondroplastic dwarfism with hydrocephalus are occasionally observed and finally there is always a large number of patients with hydrocephalus particularly of the communicating type in which a cause can never be established

Subdural Hematoma in Infancy This is a not infrequent cause of a symmetric enlargement of the skull It may occur in several circumstances (1) trauma to the head at birth or later (2) with bleeding diseases or in poorly nourished sickly infants some of whom are said to have had scurvy In acute subdural hematoma the symptoms are the same as those described in Chap 255 on head injury In the chronic subdural hematoma of infancy the initial symptoms are usually irritability vomiting and seizures Later the cranium enlarges symmetrically as a rule even though the subdural hematoma is unilateral X rays of the skull even years later will reveal that a characteristic enlargement of the middle cranial fossa has occurred followed later after resorption or removal of the clot by thickening of the skull and enlargement of the frontal and ethmoidal sinuses (Davidoff and Dyke)

Macroencephaly This is a rare cause of enlargement of the head The brain is malformed and greatly increased in size specimens weighing over 2,500 Gm have been recorded Mental retardation feebleness of movement and enlargement of the head with small ventricles are the criteria for clinical diagnosis The detailed pathologic process is variable and the causes are probably multiple

The *diagnosis* of hydrocephalus is usually established by injecting air directly into the dilated ventricles In the infant this is usually done by inserting a needle through the lateral border of the anterior fontanel The subdural space can also be entered during this maneuver and the aspiration of it will rule out chronic subdural hematoma If *the cortical mantle is thin or the subarachnoid space* dilated cerebrospinal fluid may be obtained and mistaken for subdural fluid In the older child or adult pneumoencephalography burr holes and inspection of the dura must be used Macroencephaly is distinguished by the small lateral and third ventricles The entrance into the ventricles of air that has been introduced into the lumbar subarachnoid space or the passage of a dye such as phenol sulfonphthalein injected into the lateral ventricles to the lumbar subarachnoid space is of help in determining whether or not the hydrocephalus is due to an obstruction in the ventricle system (*obstructive* hydrocephalus) or *is nonobstructive* (also called *communicating* hydrocephalus) The latter is usually due to obliteration of subarachnoid space over the medulla pons and midbrain by a fibrosing meningitis Thrombosis of the superior sagittal sinus may cause headache and elevated intracranial pressure but does not expand the ventricles

The *treatment* of these conditions is relatively unsatisfactory If the hydrocephalus has stabilized *i e the head is no longer enlarging no treatment* should be undertaken If the head is large and the patient is mentally enfeebled or has other serious malformations surgical therapy is ill advised If the hydrocephalus is definitely progressive but the patient s neurologic status is good a number of operative procedures should be tried With obstruction of the aqueduct or fourth ventricle the Torkildsen procedure (short circuiting the fluid *through a tube from the occipital horn of the lateral* ventricle to the cisterna magna) has given the best results Some cases of communicating hydrocephalus have been helped by procedures which shunt the cerebrospinal fluid into the mastoid ureter fallopian tube peritoneal cavity jugular vein or spinal epidural space The treatment of chronic subdural hematoma is repeated percutaneous aspiration by needle and in some cases removal of the *membranes enclosing the subdural hematoma* must be carried out at a later stage Nothing can be done about macroencephaly

Deformity of the Skull The usual cause of a severely misshapen head in the adolescent or adult is cranial dysostosis The cause of this premature fusion or synostosis of one or several cranial sutures is unknown but the most plausible explanation is that the mesenchymal tissues which form the cranial bones *are defective the premature ossi*fication being secondary The occasional association of cranial synostosis with syndactylism (Apert s syndrome) has been cited in support of this hypothesis The developmental defect and synostosis are believed to date from intrauterine life Closure of the sagittal suture results in an elongated doli

the suture lines close (3) the existence of external pressures against the skull In addition a depressed fracture cephalohematoma craniocele or tumor may cause a localized cephalic deformity

It is the constant outward pressure of the developing brain which causes the head to enlarge rapidly in the first months and years of life The proof of this observation is that any disease which destroys a substantial portion of the cerebral hemispheres in infancy will result in microcephaly and conversely excessive intracranial pressure as from hydrocephalus or chronic subdural hematomas enlarges the head to an abnormal degree Focal lesions e g destruction of one hemisphere result in smallness of the skull on that side and a unilateral subdural hematoma enlarges it Regarding premature closure of the sutures (synostosis) it should be noted that this may occur without abnormality of the brain If all sutures close cranial expansion is prevented or if some sutures close and others remain open enlargement will occur only at the latter sites and the skull then becomes deformed A flattening of one side of the head (plagiocephaly) often is found in defective or sick infants who lie in one position for prolonged periods of time The weight of the head against the bed prevents part of the skull from expanding but the cranial capacity is usually undiminished for there is a bulge in another direction usually on the opposite side This deformity will persist if the abnormal positioning continues beyond the period of maximal brain growth Congenital depressions have been observed to result from the prolonged pressure of a fetal hand or foot against the cranial bones in utero

Macrocephaly (Enlargement of the Head) A general enlargement of the head must be distinguished from a misshapen head one that is enlarged in one direction only Three different conditions must be considered in the differential diagnosis—infantile hydrocephalus infantile chronic subdural hematoma and macroencephaly

Hydrocephalus This most frequent cause of enlargement of the head is the only condition in which there is enormous enlargement The majority of severely hydrocephalic infants die within a few months or years and are not seen by internists but a few linger on Sometimes the hydrocephalus becomes arrested and there is a long term survival Hydrocephalus was discussed in Chap 31 Cerebrospinal Fluid and here it is necessary only to point out some of the characteristic changes which the skull undergoes Prominence of the frontal and parietal eminences (hydrocephalic bossing) depression of the orbits relatively low position of the ears dwarfing of the face by the broad expanse of forehead and wide eyed" or staring expression with sclera showing between the upper lid and iris are obvious in the more advanced cases The skin of the scalp is thin and tightly stretched and the subcutaneous veins are prominent The anterior fontanel is nearly always open and full and usually the posterior one which should be closed by the fourth or fifth month remains open During infancy percussion of the head in the parietal region with the finger gives a cracked pot or ripe melon sound (Macewen s sign) With a bright flashlight there may be *excessive transillumination* of the head in the region of the cerebral hemispheres a finding noted in severe degrees of hydrocephalus in hydranencephaly (a condition in which there is a combination of developmental defect in the cerebral tissue and hydrocephalus) and rarely in severe destructive lesions of the brain that occur in utero or in early life (The cerebrospinal fluid does not impede the transmission of light as does brain tissue) Similarly the posterior fossa will transilluminate in the type of hydrocephalus caused by atresia of the foramens of Magendie and Luschka in which the recesses of the fourth ventricle are greatly dilated In older children and adults with large heads due to hydrocephalus neither Macewen s sign nor transillumination may be demonstrated Roentgenograms confirm the enlargement and altered configuration of the head and also show the characteristic digital markings in the frontal and parietal bones

The chronic hydrocephalic syndrome consists of mental dullness slight ataxia mild pyramidal tract signs and impaired vision In the late stages of advancing hydrocephalus the child is usually bed fast seemingly unable to support the enormous head upon the frail body He becomes emaciated his cry is shrill he is blind and has pale optic disks the legs are moved feebly if at all the tendon reflexes are lively and Babinski signs are easily elicited in many cases Ulceration of the scalp may occur Death ultimately results from inanition and infection usually during the first year of life However some patients live on for years and may eventually come under the care of the general physician Not infrequently the illness is terminated by *Escherichia coli Bacillus pyocyaneus* or other unusual types of meningitis

Congenital hydrocephalus may appear years after birth If the sutures have already closed (after the twelfth year) the head cannot enlarge and the hydrocephalus is poorly tolerated Increased intracranial pressure with papilledema vomiting and mental dullness are the usual signs

The usual causes of hydrocephalus are

1 *Arnold Chiari malformation with spina bifida and meningomyelocele*

2 *Atresia or stenosis of the aqueduct of Sylvius* with obstructive hydrocephalus and a small normal appearing posterior fossa This may be an inherited

platybasia fusion of the atlas and occiput or of vertebras (Klippel Feil syndrome) or congenital dislocation of the atlas are the consequence of a malformation of the spine itself and the enclosed spinal cord may or may not be involved Others such as spina bifida occulta spinal meningocele or myelomeningocele or dysraphism involve the whole neural tube including spinal cord investing meninges vertebral bodies and even the overlying skin and subcutaneous tissues

In many of these patients the neurologic defect which appears in infancy does not shorten life in others it becomes manifest only during adult life

Primary Malformations of Vertebras These are most frequent in the cervicooccipital region

The Klippel Feil Deformity This abnormality consists of maldevelopment and fusion of two or more cervical vertebrae resulting in a short neck of limited mobility The hairline is low often at the level of the first thoracic vertebra There may or may not be associated neurologic symptoms or signs The importance of the spinal deformity lies in its frequent association with other abnormalities especially platybasia and syringomyelia

Platybasia (Basilar Impression) In this mal development of the base of the skull there is invagination of the occiput and upper cervical spine into the posterior fossa Often the foramen magnum itself is imperfectly developed or the atlas and occiput are fused The exact teratogenesis of this anomaly is uncertain It may in some instances be asymptomatic but frequently there is crowding distortion or compression of the spinal cord medulla and cranial and spinal nerves The resulting *clinical* picture is variable Symptoms may be present from early life or may begin in late childhood adolescence or even adult years Early symptoms in patients old enough to give a history consist of dizzy" or weak" spells occipital neuralgia transient paresthesias in the occipital region neck or arm double vision facial paresthesias and deafness cerebellar ataxia and spastic weakness of the legs The symptoms may at first be intermittent and at any time in the course of the illness may be aggravated by straining moving the head or placing the head and neck in certain positions Inspection alone provides a clue to diagnosis The whole configuration of the head and neck is unnatural The neck is short the ears and hairline are low neck movements are obviously restricted and the normal cervical lordosis is lost or greatly exaggerated sometimes to the extent that the occiput lies almost on the upper dorsal spine and shoulders

Platybasia and these related anomalies of the spine should be suspected in all cases presenting progressive cerebellar brain stem and cervical cord syndromes Many of these patients have been diagnosed as having multiple sclerosis The clinical suspicion of platybasia can be confirmed by a true lateral roentgenogram of the skull In such a projection the extension of a line drawn from the hard palate and posterior border of the foramen magnum (Chamberlain s line) and another through the spine and body of the first cervical vertebra (Bull s line) instead of being more or less parallel as they normally are intersect when extended This has proved to be the most useful measurement Chamberlain s basal angle obtained by drawing lines along the hard palate and clivus is greater than 135 in *platybasia Also when visible the odontoid process* may project above Chamberlain s line In Towne s view of the skull a malformation or coarctation of the foramen magnum is occasionally found An acquired form of platybasia occurs with rickets and Paget s disease It is usually asymptomatic

The Arnold Chiari Malformation This condition in which medulla and inferior posterior portions of the cerebellar hemispheres project caudally through the foramen magnum often to the level of the second cervical vertebra has already been mentioned as a cause of hydrocephalus It is nearly always associated with a spinal meningocele or *myelomeningocele and often there are deformities* of the cervical spine and cervicooccipital junction The symptoms of hydrocephalus dominate the clinical picture in infants but in milder cases there may develop during adolescence or adult years any one of the several syndromes already described under platybasia When platybasia and the Arnold Chiari malformation coexist it is generally impossible to decide which of the two is responsible for the clinical findings

The cause of the Arnold Chiari malformation itself has been the subject of speculation It has been suggested that the hydrocephalus is primary and that the displacement of the medulla and cerebellum through the foramen magnum is secondary to pressure from above The close relationship to spinal myelomeningocele casts doubt on this explanation The more generally accepted hypothesis is that the associated myelomeningocele causes downward traction on structures in the posterior fossa because *of fixation of the cord to the vertebral* column prior to the period when the growth of the vertebral column outstrips that of the spinal cord The cerebrospinal fluid then flows from the fourth ventricle into the cervical canal cannot reenter the cranial cavity and therefore is not reabsorbed Also the aqueduct of Sylvius is elongated and sometimes critically narrowed (traction stenosis) which may itself account for the hydrocephalus This is not the mechanism in all cases however for examples of the Arnold Chiari *malformation* have been observed without evidence of myelomeningocele Dysraphism of the spinal cord which resembles syringomyelia may accompany both platybasia and

chocephalic head to which the term *scaphocephaly* is applied When the coronal suture fuses prematurely the growth is restricted in the anteroposterior diameter and only lateral and to a lesser extent vertical enlargement may occur This condition is called *brachycephaly* (wide skull) or *acrobrachycephaly* Synostosis of all sutures leaves the cranium small but usually with the greatest growth in the vertical direction the so called *oxycephaly* or *turrencephaly* *Plagiocephaly* refers to an asymmetric deformity of the skull which may be due to synostosis of a single coronal suture or to the application of some external force In *Crouzon's craniofacial dysostosis* acrobrachycephaly is associated with a beak nose This condition is inherited as a mendelian dominant In *Apert's syndrome* webbed or mitten fingers and toes are combined with the Crouzon's defects *Hypertelorism* as described by Greig in 1924 is a rare deformity characterized by wide separation of the eyes and a flat retracted bridge of the nose Mental retardation frequently accompanies the deformity The primary abnormality has usually been ascribed to an abnormally large lesser wing of the sphenoid bone In several instances a dominant mode of inheritance has been found

The most serious complication of synostosis of sutures is a gradual increase in intracranial pressure which occurs during the most active growth period of the brain This tends to be less marked in patients with scaphocephaly than in those with acrobrachycephaly In these patients the orbits are shallow and the eyes bulge Headache divergent strabismus papilledema optic atrophy and later blindness nystagmus mental retardation and behavioral abnormalities are the most striking clinical manifestations Usually the patients require medical attention within the first 2 or 3 years of life though it may be needed later In roentgenograms of the skull one observes the primary suture involvement prominence of convolutional markings and a depression and smallness of the sella turcica

In the absence of increased intracranial pressure the diagnosis of premature closure of the sutures should always raise the suspicion of defective growth of the brain (see below Microcephaly)

The treatment of primary craniosynostosis is surgical and if it is to be effective in preventing permanent injury to the brain it should probably be carried out early in life particularly if one has any intention of lessening the skull deformity The operative procedure is one of making artificial suture lines by removing pieces of bone and inserting a plastic material in their place to prevent regrowth Occasionally this results in a striking improvement in mental function and behavior even in an older child in whom the diagnosis had not been made early in life In other cases progression of the illness is halted Failure to improve even when surgery has been performed early suggests in certain instances that the brain defect is independent of the cranial abnormality

Microcephaly This term is used to designate any condition in which there is an abnormally small head An occipitofrontal circumference of less than 19 in beyond the age of ten years is given as the dividing line between normal and abnormal Microcephaly is accompanied by a reduction in the mass of the brain and two types of pathologic change have been reported There is one form in which the growth disturbance appears to be the sole factor the brain except for its smallness has a normal appearance This is called *microcephaly vera* The other is a focal arrest of growth due either to embryonal failure in development of a part of the cerebral hemisphere (*schizencephaly*) or to an acquired disease which has resulted in destruction of one or both of the cerebral hemispheres (*encephaloclastic microcephaly*)

Microcephaly Vera This condition may occur in several members of one generation of a family and can often be linked to a recessive gene The head tends to be extraordinarily small usually measuring 15 in or less in circumference It is usually of symmetric shape and owing to the lack of frontal prominence resembles the skull of a monkey The ears are large and often malformed The clinical picture varies All patients show simple mental retardation of moderate or severe degree Seizures and quadriparesis have been described in some patients but in the authors experience are much less frequent than in the other forms of microcephaly Those cases with focal arrest of growth or destruction of cerebral tissue schizencephaly and encephaloclastic microcephaly exhibit a wide variety of clinical findings The mental state in the most severe cases is usually that of an idiot and all cerebral functions fail to develop In fact the cerebral hemispheres may be represented only by membranes filled with clear or yellowish fluid *hydranencephaly* In others in which the cerebral defect is restricted to one cerebral hemisphere or part of a hemisphere there may be hemiplegia with a small arm and leg gross hemianesthesia homonymous hemianopia and seizures with lesser degrees of mental backwardness The skull on the side of the damaged hemisphere is smaller and in roentgenograms the frontoparietal bones are thick the middle fossa is shallow and the paranasal sinuses are enlarged

Abnormalities of the Spine of Neurologic Significance

There is a remarkable variety of neurologic syndromes which include an abnormality of the vertebral column Some of these like hemivertebra

which connect them to the skin provide free access for bacteria and are often a source of abscess and recurrent meningitis Evidence of such tracts should be sought in every instance of meningitis in children and adolescents especially when infection has recurred

There are in addition other *congenital cysts* and *tumors* which may produce progressive symptoms and signs by compressing the spinal cord or by implicating nerve roots

DIASTEMATOMYELIA This is another unusual abnormality of the spinal cord Here a bony spicule or ridge protrudes into the spinal canal from the body of one of the thoracic or upper lumbar vertebrae If the bony abnormality is in the thoracic region there will be duplication of or splitting of the spinal cord (diplomyelia) As the vertebral column grows traction is exerted on the less rapidly growing cord The stretched spinal cord is injured ("traction myelopathy") with classical manifestations of urinary and fecal incontinence and sensorimotor dysfunction in the legs Some degree of spina bifida is reported to have occurred in more than half the cases The diagnosis can be made by roentgenograms and myelogram and the bony spicule removed by surgery

These spinal abnormalities are of particular interest to internists when they begin to produce symptoms for the first time in an adolescent or adult Several clinical syndromes have been delineated (1) Progressive spastic weakness of the legs during late childhood or adolescence in a patient known to have had a meningocele or myelomeningocele Presumably the spinal cord which is securely attached to the lumbar vertebrae is stretched during the period of rapid lengthening of the vertebral column (2) An acute cauda equina syndrome following some unusual activity or incident e g rowing or a fall in a sitting position in patients who have had an asymptomatic or symptomatic spina bifida or meningocele The implicated sensory and motor roots are believed to be injured by sudden or repeated stretching Weakness of bladder control impotence (in the male) numbness of feet and legs or foot drop comprise the clinical syndrome (3) Syringomyelia—cf p 1675 (4) Progressive cauda equina syndrome due to a lipoma or dermoid in the lumbosacral region

Malformations of the Extremities

A variety of primary skeletal defects such as absence of or increase in number of digits or extremities fusion or webbing of digits (syndactylism) deformity of digits or limbs or abnormalities of size have neurologic import for they tend to be associated with malformations of the central nervous system For example *syndactylism* is frequently combined with oxycephaly (*Apert s syndrome*) In *mongolism* the fifth digit is unusually short and curved the hands are broad and simian like and there is usually only a single transverse crease in the palm In arachnodactyly the digits are long and tapering a condition frequently linked to disease of the aorta and congenital heart disease and to dislocation of the lens (cf Marfan s syndrome p 1690)

Shortening of all the extremities with normal growth of the trunk is characteristic of achondroplasia In Morquio s syndrome both the trunk and the limbs are short and deformed Thus dwarfism may be importantly linked in this condition with a neurologic abnormality just as it is in cretinism mongolism and gargoylism The sufferers from these several neurologic diseases in which growth is stunted may be referred to collectively as "demented midgets" and since many of them reach adult years they must be treated by general practitioners internists and surgeons for other diseases which develop during this age period

In some cases the deformity of the extremities is the direct consequence of a congenital neuromuscular defect In fact this happens so often that whenever deformities of the limbs are known to have begun early in life one should at once evaluate the status of the nervous system In most cases of *clubfoot* (talipes equinovarus) no abnormality of the nervous system can be ascertained In a few however the deformity results from paralysis of the anterior tibial and peroneal muscles due to a primary defect in the anterior horn cells of the lumbosacral segments of the spinal cord The contracture of calf muscles is secondary Widespread weakness and contractures of many limb muscles may cause extensive deformities (*arthrogryposis multiplex* or *amyoplasia congenita*) This syndrome may also be the result of any one of several other primary neural or muscular diseases such as congenital absence of muscles muscular dystrophy and rarely from infantile motor neurone disease (*Werdnig Hoffmann infantile muscular atrophy*) Reconstructive surgery and the techniques of physical medicine may permit a certain measure of rehabilitation in those cases with nonprogressive diseases However severe mental defects which are frequent in these conditions tend to discourage elaborate programs of therapy

Birthmarks and Associated Neurologic Conditions

A number of neurologic abnormalities are combined with congenital defects of skin or retina explained usually by their common ectodermal origin The terms *congenital ectodermal dysplasias congenital neurocutaneous syndromes* or *phacomatoses* (*phakos* birthmark) are used frequently to desig

Arnold Chiari malformation and manifests itself by segmental weakness atrophy areflexia and sensory loss in the arms and hands Syringomyelia may also occur This is discussed in Chap 259

Methods of treatment of platybasia and the Arnold Chiari malformation have not been entirely satisfactory If clinical progression is slight or uncertain it is probably advisable to do nothing If progression is certain and disability is increasing upper cervical laminectomy and enlargement of the foramen magnum are indicated Sometimes these procedures halt the course of the illness or result in improvement The surgical procedure must be done cautiously however for extensive manipulation of these structures may aggravate the symptoms or even cause death

Malformations Associated with a Defect in Closure of the Neural Arch There are many deformities along the posterior surface of the body that are accompanied by an abnormality in the formation of the posterior aspect of the neural arch and closure of the primitive neural tube The entire neural canal including the cranium may fail to close (*craniorhachischisis totalis*) or there may be only a minute defect in one or more of the vertebral arches demonstrable by roentgenograms (*spina bifida occulta*) The latter is said to occur in one quarter of the population It has been estimated that in approximately one of every 900 births there is a serious closure defect in the spine or more rarely in the cranium

The neural tube is closed and has been separated completely from the anlage of the skeleton by approximately the third week of intrauterine life and by three months the neural arches are completely fused along their dorsal aspect The defects under discussion must then have originated during the early weeks of embryonic life in all probability by the middle of the first month The skeletal malformations may arise at any time prior to the end of the third month The not infrequent occurrence of some of these defects in several siblings attests to their genetic origin and the data suggest a recessive mode of inheritance

Defects of this type may be found at any point along the neuraxis They are most frequent in the lumbosacral and cranial regions less frequent in the cervical region and rare in the thoracic region The character of the abnormality varies There may be an outpouching of neural elements (nerve root and cord) through a defect in mesenchymal tissue and skin (*myelomeningocele*) less often actually in less than one fifth of all cases only a thin walled cyst composed of meninges and containing no neural tissue can be found The cranial defect similarly may consist of an encephalocele with evagination of cerebral tissue and meninges through a midline defect in the membranous bones of the skull These are most often occipital in location though a few may be frontal presenting either anteriorly or inferiorly into the nasal cavity Probably the most astonishing cranial defect of all and one nearly as frequent as the myelomeningocele is *anencephaly* In this condition there is a gross defect or absence of the membranous bones of the skull the cerebral hemispheres and corpus striatum are also absent and the remainder of the brain grossly malformed Patients with severe defects of this type usually do not survive

MENINGOCELE AND MYELOMENINGOCELE Meningocele may exist alone and unaccompanied by any symptoms or signs Myelomeningocele in contrast is associated with some dysfunction of those nervous structures that lie within the wall of the sac The signs may be minimal limited to sensorimotor dysfunction of a few segments or pronounced with total paraplegia and incontinence of urine and feces Severe paralysis and wasting of muscles in the legs may result in contractures and various skeletal deformities such as *clubfoot* or *arthrogryposis multiplex congenita* (see Malformations of the Extremities further on in this chapter) Such cases show a susceptibility to decubitus ulcers and not infrequently there is infection of the sac and neighboring tissues When the defect involves only the meninges or a few roots the neurologic defect may not be apparent at birth After a year or two attention is directed toward this possibility by the discovery of contracture feebleness of movement smallness of muscles of the legs or by some urologic disorder

The decision to operate upon these infants with total paralysis of the legs and of the rectal and bladder sphincters may be questioned One must be alert to the development of hydrocephalus either before or after operation on the spinal lesion This almost always means an associated Arnold Chiari malformation as already stated Some of these cases can be helped by craniocervical decompression

OTHER ABNORMALITIES RELATED TO A DEFECT IN CLOSURE OF NEURAL CANAL These are often indicated by a small dimple in the skin or by a tuft of hairs along the posterior surface of the body in the midline These signs occur most often in the lumbosacral and occipital regions and are thought to represent failure of closure of the anterior or posterior neuropores (The pilonidal sinus in the opinion of the authors should not be included in this group) Small sinus tracts may exist at these points and are of clinical importance because they frequently connect with the central nervous system or its coverings and are not uncommonly associated with dermoid cysts at the central end of the tract These cysts most often occur in the cerebellum or in the lumbosacral regions and the sinus tracts

which connect them to the skin provide free access for bacteria and are often a source of abscess and recurrent meningitis Evidence of such tracts should be sought in every instance of meningitis in children and adolescents especially when infection has recurred

There are in addition other *congenital cysts* and *tumors* which may produce progressive symptoms and signs by compressing the spinal cord or by implicating nerve roots

DIASTEMATOMYELIA This is another unusual abnormality of the spinal cord Here a bony spicule or ridge protrudes into the spinal canal from the body of one of the thoracic or upper lumbar vertebrae If the bony abnormality is in the thoracic region there will be duplication of or splitting of the spinal cord (diplomyelia) As the vertebral column grows traction is exerted on the less rapidly growing cord The stretched spinal cord is injured ("traction myelopathy") with classical manifestations of urinary and fecal incontinence and sensorimotor dysfunction in the legs Some degree of spina bifida is reported to have occurred in more than half the cases The diagnosis can be made by roentgenograms and myelogram and the bony spicule removed by surgery

These spinal abnormalities are of particular interest to internists when they begin to produce symptoms for the first time in an adolescent or adult Several clinical syndromes have been delineated (1) Progressive spastic weakness of the legs during late childhood or adolescence in a patient known to have had a meningocele or myelomeningocele Presumably the spinal cord which is securely attached to the lumbar vertebrae is stretched during the period of rapid lengthening of the vertebral column (2) An acute cauda equina syndrome following some unusual activity or incident e g rowing or a fall in a sitting position in patients who have had an asymptomatic or symptomatic spina bifida or meningocele The implicated sensory and motor roots are believed to be injured by sudden or repeated stretching Weakness of bladder control impotence (in the male) numbness of feet and legs or foot drop comprise the clinical syndrome (3) Syringomyelia—cf p 1675 (4) Progressive cauda equina syndrome due to a lipoma or dermoid in the lumbosacral region

Malformations of the Extremities

A variety of primary skeletal defects such as absence of or increase in number of digits or extremities fusion or webbing of digits (syndactylism) deformity of digits or limbs or abnormalities of size have neurologic import for they tend to be associated with malformations of the central nervous system For example *syndactylism* is frequently combined with oxycephaly (*Apert s syndrome*) In *mongolism* the fifth digit is unusually short and curved the hands are broad and simian like and there is usually only a single transverse crease in the palm In arachnodactyly the digits are long and tapering a condition frequently linked to disease of the aorta and congenital heart disease and to dislocation of the lens (cf Marfan s syndrome p 1690)

Shortening of all the extremities with normal growth of the trunk is characteristic of achondroplasia In Morquio s syndrome both the trunk and the limbs are short and deformed Thus dwarfism may be importantly linked in this condition with a neurologic abnormality just as it is in cretinism mongolism and gargoylism The sufferers from these several neurologic diseases in which growth is stunted may be referred to collectively as "amented midgets" and since many of them reach adult years they must be treated by general practitioners internists and surgeons for other diseases which develop during this age period

In some cases the deformity of the extremities is the direct consequence of a congenital neuromuscular defect In fact this happens so often that whenever deformities of the limbs are known to have begun early in life one should at once evaluate the status of the nervous system In most cases of *clubfoot* (talipes equinovarus) no abnormality of the nervous system can be ascertained In a few however the deformity results from paralysis of the anterior tibial and peroneal muscles due to a primary defect in the anterior horn cells of the lumbosacral segments of the spinal cord The contracture of calf muscles is secondary Widespread weakness and contractures of many limb muscles may cause extensive deformities (*arthrogryposis multiplex* or *amyoplasia congenita*) This syndrome may also be the result of any one of several other primary neural or muscular diseases such as congenital absence of muscles muscular dystrophy and rarely from infantile motor neurone disease (*Werdnig Hoffmann infantile muscular atrophy*) Reconstructive surgery and the techniques of physical medicine may permit a certain measure of rehabilitation in those cases with nonprogressive diseases However severe mental defects which are frequent in these conditions tend to discourage elaborate programs of therapy

Birthmarks and Associated Neurologic Conditions

A number of neurologic abnormalities are combined with congenital defects of skin or retina explained usually by their common ectodermal origin The terms *congenital ectodermal dysplasias congenital neurocutaneous syndromes* or *phacomatoses* (*phakos* birthmark) are used frequently to desig

nite this general class of disorders The major syndromes include *neurofibromatosis tuberous sclerosis encephalotrigeminal syndrome* and rarely the *cerebelloretinal hemangioblastomatosis* Another variant of the latter is the *myelocutaneous syndrome* in which a vascular malformation of spinal cord and meninges is associated with a vascular nevus within the area of skin innervated by the involved spinal segments

Neurofibromatosis (von Recklinghausen s Disease) This is an inherited disease (mendelian dominant) in which spots of increased skin pigmentation are combined with multiple neurofibromas The pigmented spots are irregular in shape with relatively even borders vary in size from a few millimeters to several centimeters and are of brownish-coffee color (cafe au lait) They are most prominent over the trunk and especially about the pelvis Similar lesions occur in people without neurofibromatosis but in such instances are generally smaller than 2 cm in diameter and fewer than five in number The tumors arise from the neurilemmal sheath (Schwann cells) and fibroblasts of the peripheral nerve They are usually multiple and vary in size from minute lesions to large tumors several centimeters in diameter The majority are smoothly rounded or lobulated soft or firm and can sometimes be seen or felt along the course of a peripheral nerve Often they sink into the subcutaneous fat on gentle pressure Like the pigmented lesions the tumors are more frequent over the trunk than on the extremities The pigmented areas of skin may be visible in infancy though usually they become increasingly apparent with age the tumors of nerve sheaths are often not demonstrable early in life Most of the tumors in neurofibromatosis are asymptomatic but occasionally if they attain a large size or occupy an unusual position they may produce symptoms by pressing upon contiguous structures Tumors of the spinal nerves may compress the spinal cord and at the same time extend through the intervertebral foramens to form a large mass in the posterior mediastinum (dumbbell tumors) Acoustic neurinomas usually bilateral in patients with neurofibromatosis may produce deafness and symptoms and signs of a cerebellopontine angle tumor Other histopathologic types of tumor (meningioma glioma) are encountered more frequently in neurofibromatosis than in the general population Most of these tumors are rare in infancy and childhood though glioma of the optic nerve is an exception to this clinical rule The latter condition should always be considered in the differential diagnosis of unilateral (rarely bilateral) blindness proptosis and extraocular muscle paralysis in childhood especially if there are signs of von Recklinghausen s disease Enlargement of the optic foramens demonstrable by roentgenogram is a valuable aid in diagnosis Pheochromocytoma is an infrequent accompaniment of the disease In about 5 to 10 per cent of cases of neurofibromatosis one of the tumors will become sarcomatous

Fibrous dysplasia congenital vertebral anomalies local gigantism of an extremity subperiosteal bone cysts and pseudoarthrosis of the tibia may be associated with neurofibromatosis Any of these can lead to scoliosis a common skeletal deformity in children with this disease so that neurofibromatosis must be added to the list of neurogenic kyphoscolioses (the others are syringomyelia Friedreich s ataxia and poliomyelitis) Stenosis of the aqueduct with obstructive hydrocephalus is at times observed in neurofibromatosis Also mental retardation is rather common in families with von Recklinghausen s disease though its pathogenesis is not at all understood Spina bifida hypospadias glaucoma and elephantiasis are occasionally seen

There is no treatment for the disease other than excision of tumors which cause pressure on a nerve

Tuberous Sclerosis (Bourneville s Disease) This curious disease of dominant inheritance is manifested by the clinical triad of convulsive seizures progressive mental deficiency and adenoma sebaceum The latter are fine wartlike lesions predominantly in a butterfly distribution over the cheeks and forehead The individual adenomas vary in size from 0 1 to 1 0 cm and are elevated and pinkish or pinkish yellow in color In addition the skin over the lower back may be thick rough and of yellowish color (shark skin patch shagreen) The mental deficiency may be relatively stationary or progressive The seizures are usually generalized but may be focal Retinal tumors optic atrophy cataracts and hyperonchomas syndactylism spina bifida and other visible malformations may be conjoined

The lesions of the skin are pathologically fibromas and not true adenomas Some are rather vascular and suggest telangiectasia The brain lesions consist of areas of malformed cortex with extensive astrogliosis and a curious mixture of glioblasts and monster nerve cells Calcification may or may not be present Masses of subependymal glial tissue account for nodules which project into and form the candle götterings on the walls of the ventricles that are often seen in pneumograms In Bourneville s original case death was due to rhabdomyoma of the heart This lesion has been combined in some cases with vascular malformations of kidney liver adrenal glands and pancreas

The diagnosis is aided by roentgenograms of the skull Calcified nodules occur particularly in the temporal lobe The center of the nodule tends to be more densely radiopaque than the periphery

The EEG is usually abnormal but without specific pattern The cerebrospinal fluid may be normal rarely the total protein is elevated

The only treatment is symptomatic The prognosis for life beyond the third decade is poor Death may be due to seizures associated tumors or intercurrent diseases

Cerebelloretinal Hemangioblastomatosis (Lindau s and von Hippel s Disease) This condition is discussed here though the skin is seldom involved As the name implies the syndrome consists of a vascular malformation of retina and cerebellum The retinal lesion usually has the characteristics of a malformation whereas the cerebellar lesion consists of a slowly growing cystic tumor The clinical symptoms and signs consist of progressive cerebellar ataxia headache and papilledema Polycythemia of undetermined etiology has been observed in many cases and has in a few instances disappeared after excision of the tumor Rarely do these tumors appear before adolescence Some cases are familial (mendelian dominant)

This condition is often associated with malformation of other organs especially with visceral tumors Angiomas of the liver cysts of the pancreas and kidneys and tumors of the epididymus and kidney which have been the cause of death in some cases are the major parts of the syndrome Pheochromocytomas have been described in this and in other of the phakomatoses Syringomyelia has been observed in a few cases and if a careful search is made a hemangioblastoma can often be found in relation to the syrinx at some level

The cerebellar hemangioblastoma demands surgical treatment and if the nodule of tumor is found in the wall of the cyst and is excised the results can be excellent

Encephalotrigeminal Syndrome (Sturge Weber Dimitri Disease) This curious disease consists of capillary or cavernous hemangiomas within the cutaneous distribution of the trigeminal nerve and of a predominantly venous hemangioma of the leptomeninges If the skin lesion is within the area of supply of the ophthalmic division of the trigeminal nerve the occipital lobes are more commonly involved whereas a facial nevus is more often associated with involvement of the parietal and frontal lobes The intracranial or cutaneous lesion may occur separately

Pathologically in addition to the large number of abnormal blood vessels in the meninges the cortex is destroyed and in some cases a band of calcium develops within the lesion This band following the convolutional pattern as it does is responsible for the characteristic roentgenographic picture

The first neurologic symptom is usually a focal seizure on the side opposite the skin lesion Transient postictal (Todd s) paralysis may follow the seizure Sensorimotor paralysis or permanent visual field defect the most frequent findings may be either of insidious onset and slow progression or apoplectic sometimes with bloody spinal fluid indicating rupture of a subarachnoid vessel In fact repeated hemorrhages into the meninges have been reported Possibly occlusion of cortical vessels will in certain instances be responsible for neurologic deficits Blindness in the eye on the side of the nevus is frequent and is nearly always due to glaucoma Most patients with this malformation survive for many years often with residual mental and other neurologic defects

The lesions are usually too extensive to be treated surgically though hemispherectomy has been advised by some surgeons Anticonvulsant medication is indicated but the seizures may be difficult to control

Abnormalities of Motor Function (Cerebral Palsy)

In this category of neurologic defect a major disturbance of motor function usually nonprogressive has been present since infancy or childhood The popular term for these conditions is *cerebral palsy* The name is not altogether appropriate nor is such a crude classification of nervous disorders particularly useful from the viewpoint of the physician because it results in a collocation of diseases of widely differing etiologic and anatomic types The hereditary and acquired the intrauterine natal and postnatal diseases lose their identity Nevertheless the term has been adopted as a slogan for fund raising societies and for a major rehabilitation movement throughout the United States and it will not soon disappear from medical terminology

Clinical Approach to Motor Disturbances Which Have Developed in Infancy or Childhood

Motor abnormalities which have their onset early in life are so numerous and diverse that it is necessary to acquire some knowledge of the motor system in order to interpret them Also a classification is useful in guiding one s thinking It is helpful to attempt to categorize a given case according to the extent and nature of the abnormality

CLASSIFICATION OF DEVELOPMENTAL MOTOR ABNORMALITIES

I Spastic or rigid paralyses
- *A* Cerebral spastic diplegia and paraplegia
- *B* Infantile hemiplegia
- *C* Double hemiplegia
- *D* Quadriplegic states

II Extrapyramidal syndromes
- *A* Choreoathetosis and dystonia
- *B* Cerebellar ataxia

nate this general class of disorders The major syndromes include *neurofibromatosis tuberous sclerosis encephalotrigeminal syndrome* and rarely the *cerebelloretinal hemangioblastomatosis* Another variant of the latter is the *myelocutaneous syndrome* in which a vascular malformation of spinal cord and meninges is associated with a vascular nevus within the area of skin innervated by the involved spinal segments

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birth or during the first 6 to 12 months of life Acquired forms following an infection or thrombosis of cerebral arteries or veins usually develop later The parents may be the first to notice that movements of prehension and exploration are carried out with only one arm The affection of the leg is usually recognized later i e during the first attempts to walk

The cardinal feature of a cerebral hemiplegia and this also applies to diplegia is that it is partial the limbs will always move under certain circumstances The most satisfactory tests are the facility with which the two arms engage in manipulative prehensile and exploratory movements The latter may be examined in the first weeks of life by placing the infant on his feet and making him step forward by advancing and tipping the trunk from side to side Hand preference during the first 2 to 3 years of life should always raise a suspicion of a motor defect on the opposite side

If the brain lesion responsible for the hemiplegia is of recent onset (at birth or shortly before) and the cerebral lesion extensive one may observe sluggishness of all motor responses poor sucking reflexes difficulty in breathing and irregular pulse The tendon reflexes tend to be more active on the affected side and the plantar reflexes more definitely extensor in type than on the normal side There may be a homonymous visual field defect as shown by a neglect of dangling objects on one side or a unilateral somatic sensory loss indicated by a lesser response to tickle a vibrating tuning fork and painful stimuli The muscular tone is usually normal

An assessment of the neurologic status at the end of the first and second years reveals more clearly the extent of the motor defect The hand and fingers are clumsy and slow Often the fingers are hyperextensible and in one third of cases they exhibit athetotic movements and postures in which the wrist is strongly flexed metacarpal phalangeal joints are extended and phalangeal joints are variably flexed or extended in various sequences The adult hemiplegic attitude i e the arm adducted at the shoulder flexed and internally rotated at the elbow pronated and flexed at wrist and fingers with the thumb adducted and covered by the fingers and the leg adducted and internally rotated at the hip with the foot inverted and plantar flexed is evident at this time Contractures may be found in the hip flexors hamstrings and plantar flexors of the foot Sitting standing and walking are delayed but not so frequently as in cases of cerebral diplegia Improvement may be noticed as the child grows and matures especially if there has been a severe sensory defect Impaired sensation appears to retard motor development early in life but later is compensated for even though such patients retain their sensory defects At a more advanced age when sensory testing can be done specific difficulties of proprioception two-point localization recognition of form by feeling an object and failure to appreciate a stimulus on the involved side when one is simultaneously applied to the other side can be demonstrated in about a fourth of these cases Smallness or hypoplasia of the hemiplegic extremities (hemiatrophy) is another common finding especially during adolescent and adult years The use of a limb appears to be a necessary stimulus to its growth Hemiatrophy in the adult always means that the neurologic deficit began before growth had proceeded very far usually in childhood or before

Mental defect may be associated with infantile hemiplegia but is much more common with cerebral diplegia and with bilateral hemiplegia Convulsions occur in 35 to 50 per cent of children with congenital hemiplegia They may commence at any time of life but more often in infancy or early childhood if the disease was congenital If the hemiplegia was acquired during infancy seizures often accompany the onset They may be generalized but are frequently unilateral and limited to the hemiplegic side Often after a series of seizures the affected side will be weak for several hours or longer (Todd's paralysis)

Double Hemiplegia This term is applied to bilateral weakness of face arms and legs The arms are severely affected in contrast to their minimal affection in cerebral diplegia Difficulty with breathing sucking and swallowing is usually noted in the neonatal period if the illness began at or before birth Weakness and spasticity are apparent at an early age Opisthotonos with flexed arms and extended legs is the usual attitude and is exaggerated during periods of crying The cry itself tends to be high pitched and shrill Mental development is almost invariably retarded and such children usually never learn to sit walk or develop any effective use of the limbs The bulbar musculature is also affected Choreoathetosis blindness and seizures occur in many of the patients The head tends to be small in children with double hemiplegia reflecting the small size of the brain In other respects bilateral hemiplegia does not differ from unilateral hemiplegia

Quadriplegic States Differing from bilateral hemiplegias in that the bulbar musculature is not involved this condition is relatively rare but may result from a bilateral cerebral lesion However a spastic quadriplegia should always alert one to the possibility of a high cervical cord lesion Although this may occasionally result from cysts tumors and other malformations it is usually produced in the infant by a fracture dislocation of the cervical spine incurred during a difficult breech delivery Crothers and Putnam state that an audible snap may be heard at the time of fracture If the condition goes

III Flaccid paralyses
- A Generalized
  - 1 Cerebral type—cerebral atonic diplegia (of Foerster)
  - 2 Spinal type
    - a Infantile muscular atrophy of Werdnig Hoffmann
    - b Traumatic necrosis of spinal cord
  - 3 Other types
    - a Infantile muscular dystrophy
    - b Lipoid and glycogen storage diseases
    - c Infantile polymyositis
    - d The slack child and amyotonia congenita of Oppenheim
- B Localized (nerve)
  - 1 Brachial plexus palsies of Erb and Klumpke
  - 2 Facial palsy
  - 3 Other peripheral nerve palsies

These motor abnormalities of infancy and childhood are relatively frequent and many of the affected children reach adult years

Special Types

Infantile Spastic and Rigid Paralyses The pattern of paralysis or rigidity is important for it provides information as to the etiology and possible pathogenetic mechanism

Cerebral Spastic Diplegia (Little's Disease) In 1862 Little called attention to the concurrence of "Abnormal Parturition Difficult Labours Premature Birth and Asphyxia Neonatorum and of a spastic weakness that affected legs more than arms He emphasized the prenatal or natal origin the diplegic (legs > arms) distribution of the paralysis and the nonprogressive course Little was of the opinion that birth trauma or asphyxia caused the cerebral damage but further studies by Freud Osler Ford and others have cast doubt on this explanation by showing the existence of congenital and hereditary forms The present view is that it represents a syndrome of multiple etiology and of diverse pathology

S A K Wilson distinguishes three types the paraplegic diplegic and the generalized and pseudobulbar These differ from one another only in respect to the severity of affection of the arms and bulbar musculature Pure paraplegias and pure pseudobulbar cases are relatively rare Usually all four extremities are involved the legs much more than the arms As a rule the abnormality is recognized at birth or soon thereafter by some abnormality of breathing sucking and swallowing color of mucous membranes or responsiveness These latter signs may indicate either a congenital defect of the nervous system or birth injury The stiff awkward movements of the legs maintained in an extended adducted posture attract attention at this time or in the ensuing weeks Seizures occur in some cases and it is not uncommon to observe a delay in all the normal developmental sequences especially those which depend on the motor system Once walking is attempted the characteristic stance and gait become manifest The legs are advanced stiffly in short steps each describing part of the arc of a circle adduction is often so strong as to lead to actual crossing (scissors gait) with lower legs slightly splayed out and the feet flexed and turned in the heels no longer touching the ground The legs tend to be thin but the muscles are not markedly atrophic as in infantile muscular atrophy and dystrophy Passive manipulation of the limbs reveals marked spasticity in the extensors and adductors and also slight contracture of calf muscles The hands and arms may be little if at all affected but in many cases there is awkwardness and stiffness of the fingers and in a few pronounced weakness and spasticity Speech may be well articulated or noticeably slurred and often the face is set in a spastic smile The deep tendon reflexes are exaggerated those in the legs more than in the arms and the plantar reflexes are extensor Usually there is no disturbance of sphincteric function though delay in acquiring voluntary function is usual Athetotic postures and movements of the face tongue and hands are present in some cases and may actually conceal the pyramidal weakness Ataxic and hypotonic forms also exist The mentality ranges from normalcy to idiocy

Surprisingly little information has been obtained concerning the cause mechanism and morbid anatomy of this syndrome The claim that birth injury is responsible has been challenged and the existence of an antenatal lesion can no longer be doubted A familial variety of spastic diplegia is now well documented but such a genetic determination applies to only a minority of cases and the progressive nature of the illness readily distinguishes this disease from the conditions under discussion (see p 1675) The brain has appeared grossly normal in some instances and the only microscopic abnormality has been an absence of Betz cells and a poorly myelinated corticospinal tract It is as though the corticospinal system had failed to develop In others a diffuse loss of nerve cells and gliosis of cerebral cortex (mantle sclerosis) has been found Shrunken atrophic convolutions with or without cavitation of white matter (ulegyria) a restricted form of which may involve only a few convolutions has probably been the most frequent pathologic finding The pathologic findings give little information as to the original process except that it must have occurred after cerebral development was nearly complete

Infantile Hemiplegia In this not uncommon condition of infancy and childhood a functional difference between the two sides may be noticed at

deformed walking on the heels or side of the foot is more common than the "toe walking" of the cerebral diplegic Movements may also be ataxic and tremors are not uncommon A retardation of motor development is the rule in these cases Upright posture and walking may in fact never be acquired or may be delayed until the age of three to five years in severe cases but thereafter more or less effective locomotion is possible The tendon reflexes are not consistently abnormal plantar reflexes are characteristically flexor though they may be difficult to interpret because of the continuous play of flexor and extensor movements of the toes The various sensory pathways usually function normally

It is because of the motor and speech impairment that patients are many times erroneously classified as mentally defective No doubt in some patients this evaluation is correct but others retain adequate intellectual function and can be educated With growth and development new postures and new motor capacities are acquired The less severely affected patients can make successful occupational adjustments However the severely handicapped patients even with the help of rehabilitation clinics and corrective orthopedic operations rarely achieve a degree of motor control that will permit them to lead an independent existence One sees these unfortunate individuals in public places bobbing and weaving as they walk along

The most frequently observed pathologic change in the brain has been a curious whitish marblelike appearance of the putamen thalamus and cerebral cortex These whitish strands represent foci of nerve cell destruction and gliosis with a peculiar condensation or formation of myelinated fibers (hypermyelination) Oscar and Cecile Vogt who first described this condition called it *etat marbre* or *status marmoratus* They attributed it to neonatal asphyxia, but the hypoxic factor is far from established

The *neurologic sequelae* of *kernicterus* are of importance here and are encountered not infrequently in adults It is true that the majority of infants who suffer this disease die within the first week or two of life and those who survive are mentally retarded deaf and totally unable to sit stand or walk so that the tendency is always to put them in homes for the feebleminded It is only the exceptional patient obviously less damaged who is mentally normal or at most only slightly backward These are the ones who exhibit a variety of motor disorders as they grow older the most frequent being mild ataxia or choreoathetosis which involves the face and arms A few have also shown rigid limbs and a picture not too different from that of cerebral spastic diplegia with involuntary movements Kernicterus should always be suspected if an extrapyramidal syndrome is accompanied by bilateral deafness and ocular palsies The neuropathology in these milder surviving cases consists of nerve cell loss and gliosis in the subthalamic nucleus of Luys the globus pallidus thalamus Ammon's horn and oculomotor and cochlear nuclei No one explanation of the neurologic lesion has been accepted Elsewhere we have postulated severe liver damage and hyperbilirubinemia as a cause of the brain disease but this hypothesis is unproved Others attribute the brain damage to hypoxia

Congenital Ataxia The combination of cerebral diplegia with cerebellar ataxia has already been mentioned These are cases in whom difficulty in standing and walking cannot be attributed to spasticity or paralysis Incoordination similar to that seen in cerebellar disease and hypotonia are the principal findings The motor defect may be so great that the child is never able to sit or stand the muscles are of normal size and voluntary movements though weak are possible in all the limbs In less severe cases sitting standing and walking are merely delayed and with advancing years cerebellar ataxia and tremor become manifest Relative improvement may occur as the child grows older The tendon reflexes are present and the plantar reflexes are either flexor or extensor Many of these patients suffer a degree of amentia and retardation of speech development that results in their placement in homes for the feebleminded In relatively few of the recorded cases has the pathology of this condition been studied Aplasia or hypoplasia of the cerebellum has been reported only a few times X ray radiation of the abdomen of a parturient woman during the first trimester of pregnancy has resulted in cerebellar hypoplasia in a few cases A cerebral and cerebellar lesion may coexist which is the reason for their classification as cerebrocerebellar diplegias

Aside from the congenital ataxias some of which are cerebellar others probably of cerebral type there are other forms of ataxia which have an acute onset and which persist during adolescence and adult life Batten has written informatively on this subject calling those forms the acute cerebellar ataxias of childhood Some are sequelae of an infection (a postinfectious encephalitis especially postvaricella) and a few may be due to virus infections which affect the cerebellum more than other parts of the nervous system Hyperthermia with temperatures over 106 F may result in extensive destruction of Purkinje cells and ataxia Cerebellar tumors and demyelinative and lipoid storage diseases also occur at this age and may at times give rise to cerebellar ataxia Labyrinthine injury resulting from streptomycin therapy and poly

unrecognized recurrent contusion of the spinal cord may result from handling the infant there being excessive mobility of the vertebral column If the upper cervical cord is severely damaged respirations may be difficult and signs of lower brain stem dysfunction may also appear Traction and stabilization of the cervical spine by orthopedic measures may prevent further damage and some improvement may occur but complete recovery is unusual with this condition

Similarly in *paraplegia* with weakness or paralysis limited to the legs the lesion may be cerebral or spinal Sphincter disturbances and a definite loss of somatic sensation below a certain level on the trunk should always favor a spinal localization Congenital cysts tumors and diastematomyelia are more frequently found in cases of paraplegia than of quadriplegia

The *etiology pathogenesis* and *morbid anatomy* of infantile cerebral hemiplegia bilateral hemiplegia and quadriplegia are not well understood Birth injury has been invoked as a leading cause and there is no doubt that prolonged labor delay in breathing bulging fontanel bloody cerebrospinal fluid periods of apnea and cyanosis occur with greater frequency in a series of hemiplegic infants than in any other group of infants Also birth injury is more frequent in hemiplegic than in diplegic cases The mechanism of the injury is not known In the majority of patients the birth trauma is not due simply to the direct application of force to the cerebral hemispheres Hypoxia due to cardiac arrest or interference with fetal circulation at the time when the brain was compressed may be responsible for the lesions The hemisphere opposite the hemiplegia may be small a veritable miniature of normal the cortex is thin depleted of nerve cells and gliotic and the thalamus and corticospinal tract are reduced in size In others a circumscribed encephalomalacia with shrinkage of convolutions gliosis or cavitation of white matter and basal ganglions have been found Central *lobar sclerosis* with destruction of the white matter and sparing of the cortex or multiple cavities in the white matter have been observed in a few cases It must be assumed that many of these abnormalities have been acquired during intrauterine life or at birth but their cause and pathogenesis are unknown They appear to represent forms of *pseudoporencephaly* Some may be due to narrowing or occlusion of the carotid artery (sometimes demonstrated in an arteriogram) or Sylvian vein Congenital neurosyphilis and toxoplasmosis have been established in others Prematurity may be a contributing factor and in some a history of vaginal bleeding during pregnancy has been recorded Developmental abnormalities of the brain have been discovered in a few cases

Congenital Extrapyramidal Syndromes in Infancy and Childhood The spastic and rigid cerebral diplegias discussed above shade almost imperceptibly into the extrapyramidal syndromes Many such cases can be found in every cerebral palsy clinic and they appear from time to time in adult medical clinics Pyramidal tract signs may be completely absent and the inexperienced student familiar only with the pure cerebral spastic diplegia syndrome is always puzzled as to their classification Some extrapyramidal cases of this type undoubtedly are attributable to the same pathologic processes as cerebral spastic diplegia and attest to the diverse clinical manifestations of these states others represent separate diseases such as erythroblastosis fetalis with kernicterus In the interest of being able to state accurately the probable pathologic basis and future course of these illnesses it is desirable to separate the extrapyramidal syndromes due to prenatal and natal diseases which usually become manifest during the first year of life from the acquired postnatal syndromes such as familial athetosis dystonia musculorum deformans and cerebellar ataxia The latter will be discussed in Chap 259 Degenerative Diseases of the Nervous System

Congenital Choreoathetosis (Double Athetosis) Probably the most frequent representative of this group this condition is like the spastic states in that it may not be recognized at birth but only after several months have elapsed The nature of chorea and athetosis has been discussed in Chap 26 Disturbances of the Motor System—Abnormalities of Posture Involuntary Movements All combinations of chorea athetosis hemiballismus and even dystonia may be found in a single case or one or another type of movement disorder may predominate However in all instances there is a defect in voluntary movement

Choreoathetosis in infants and children varies in severity In some the disorder is so mild that the abnormal movements are misinterpreted as restlessness or the fidgets in others every voluntary act is rendered ineffective by these involuntary movements leaving the patient nearly helpless The tongue may extrude itself from the mouth with constant drooling and the face is contorted in a never ending series of grimaces Speech is slurred inarticulate and punctuated by grunts and hideous throat sounds The hands and arms are engaged in a constant play of writhing twisting movements and all attempts to use the limbs result in a slow spreading spasm of the entire limb or all the musculature (intention spasm) Bizarre postures may be assumed The arms may be carried in a flexed or extended position in front of or behind the body and the legs may be extended The feet may be

ducted or extended posture This state of contracture of the limbs in infants is called *arthrogryposis* already referred to above It may be caused by either a primary muscular disease or a defect of the central nervous system

Brachial plexus palsies well known complications of dystocia usually result from forcible extraction of the fetus by downward traction on the shoulder in a breech presentation or from traction and tipping of the head in a shoulder presentation The upper brachial plexus and roots of the fifth cervical or the lower plexus and roots of the seventh and eighth cervical and first thoracic nerves suffer the brunt of the injury Sometimes the entire plexus is involved The upper plexus injuries (*Erb s plexus syndrome*) are estimated to be twenty times more frequent than lower (*Klumpke plexus syndrome*) according to Ford who has examined more than 200 cases of this type There should be no difficulty in distinguishing these plexus injuries from the preceding motor disorders The paralysis is restricted and complete The condition is nearly always unilateral though a few cases with bilateral involvement have been reported The infant with Erb s palsy lies in a characteristic position the affected arm is adducted and internally rotated at the shoulder and extended at the elbow The deltoid spinati biceps brachioradialis and upper pectoral muscles are paralyzed The diaphragm on the side of the palsy instead of descending with each inspiration moves paradoxically and the efficiency of pulmonary ventilation may be greatly reduced During spontaneous movements and in the Moro reflex the affected limb is motionless The grasp reflex is preserved in upper plexus injuries The biceps and supinator reflexes are absent and the triceps is present but one cannot count on these reflexes for they may normally be difficult to elicit In the Klumpke plexus injury the muscles of the hand and forearm are paralyzed whereas the function of the shoulder abductor and external rotators and elbow flexors is preserved The limb reposes in a flexed position across the trunk and the grasp reflex is absent There is often an associated Horner s syndrome The remainder of the musculature is active The pathology of these plexus injuries has not been carefully studied From the few reports it appears that the traumatic lesion involves motor roots at their junction with the brachial plexus In some cases the roots are virtually torn from the spinal cord and the matter may be damaged The treatment of Erb s palsy is immobilization of the affected arm in an abducted and flexed position Prognosis is good in the majority of cases but in severe injuries paralysis may be permanent in which instance the hand or arm fails to develop

Facial paralysis due to injury of the facial nerve immediately distal to its exit from the stylomastoid foramen by the application of forceps is another common peripheral nerve affection in the newborn The failure of one eye to close and the difficulty in suckling make this condition easy to recognize It must be distinguished from congenital facial paralysis or facial diplegia with or without weakness of the abducens muscles (*Moebius syndrome*) in which the facial nerve cells fail to develop In most cases of facial paralysis function is recovered after a few weeks in some the paralysis is permanent and may account for an asymmetry observed in later life

The Retarded Child (Feeblemindedness)

Mental retardation has been commented upon in the discussion of many of the craniospinal malformations and in the several varieties of cerebral palsy However it may also occur as the only neurologic abnormality and must therefore be discussed separately

To the pediatrician the clinical problem of mental retardation is one of the most difficult and to the parents it is one of the most dreadful of all conditions The intelligent father and mother are alert to every sign of possible brain injury and often they become alarmed about trivial deviations from their standard of normal development Slowness in sitting standing walking delay in speech any difficulty in acquiring toilet training may be seized upon as an indication of feeblemindedness The internist and general physician are apt to see only the milder noninstitutionalized patients who reach adolescence and adult years and then develop other diseases

The primary responsibility of the physician in cases of this type is to determine whether there is unmistakable evidence of maldevelopment or disease of the brain The uncertainty in evaluating cerebral function during early infancy has already been discussed From experience one learns that successive examinations over a period of months or years may be required in order to evaluate the infant s or child s capacity for mental development Above all the physician should not permit himself to be forced into a hasty or premature judgment Deafness blindness congenital speech defects (word deafness and word blindness) and motor defects must be searched for with particular care for they may account for an apparent delay in mental development by interfering with the learning processes Emotional privation and neglect may also lead to some degree of backwardness However mental retardation of significant degree cannot be explained in this way

The student confronted with a backward infant is likely to be rather bewildered by the vast array of developmental abnormalities and diseases which

neuritis or mumps are the common causes of non cerebellar ataxia which must be differentiated from the above condition

The hereditary ataxias are likely to begin at a later age and are progressive They are discussed in Chap 259

In all these congenital diseases of the brain once the symptoms and signs are well established there is no progression of the illness In fact with further maturation and training there may be improvement The clinical course thus distinguishes this whole group of diseases from those of delayed onset and progressive course (see Schilders disease lipoid storage diseases congenital neurosyphilis and toxoplasmosis which are described in Chaps 257 and 259)

The Flaccid Paralyses of Infancy and Childhood *The cerebral form first described by Foerster and called cerebral atonic diplegia* has already been mentioned in connection with congenital cerebellar ataxia It can usually be distinguished from spinal and peripheral nerve paralysis by the retention of postural reflexes (flexion of the legs at the knee and hip when the patient is lifted by placing the hands in the axillae) the preservation of tendon reflexes and the failure of mental development

The syndrome of *infantile muscular atrophy* (Werdnig Hoffmann disease) is the leading example of the category of infantile spinal muscular atrophies These little patients are usually brought to the clinic by their parents because of a difficulty with feeding and a delay of motor development About half of them are said to have been normal at birth and during the first weeks of life *Others have been slack feeble infants from the day* they were born and even before since some mothers recall a weakness also of fetal movement Slowness in feeding frequent choking constant drooling recurrent respiratory infections due to weak respiratory movements and aspiration of milk are troublesome in early life As a rule the patient prefers a supine posture his motor deficit is manifested by an inability to maintain the head in stable balance and also by the absence of the usual twisting squirming movements of the trunk The arms tend to be kept at the sides and flexed at the elbows bringing the hands over the chest The legs are characteristically abducted and flexed at the hips and knees so that the soles of the feet oppose one another (frog posture) When the infant is pulled to a sitting position the head lolls and all but the most feeble support reactions in the legs are absent Despite this profound weakness all muscle groups are capable of feeble movement until late in the course of the illness The tendon reflexes are invariably absent *Atrophy of muscle* is obscured by subcutaneous fat tissues (puppy fat) and fasciculár twitches though detectable in an electromyogram are invisible to the naked eye except in the tongue In contrast to their feeble movements these patients usually are attractive with bright sparkling eyes and lively countenance which attest to normal brain development All sensory functions are likewise retained The illness progresses slowly over a period of months or a few years and few of these patients survive until puberty Several members of a sibship may suffer the same illness but never the antecedents the pattern of inheritance usually being autosomal recessive In biopsy material or at autopsy the muscles are thin and the majority of their fibers are atrophic preserving their fetal dimensions as though improperly innervated or denervated The anterior horn cells in the spinal cord and brain stem have disappeared or are in process of degenerating and are replaced by fibrous astrocytes There is no known treatment for the disease

A few patients suspected of having infantile muscular atrophy prove with the passage of time to be merely rather inactive slack children and their motor development later proceeds at the usual rate A few may remain rather weak with thin musculature Such cases fall into the vague category of *amyotonia congenita* described by Oppenheim Brandt and others or into the group called *benign congenital hypotonia* (Walton) or *benign congenital myopathy* (Turner) Probably several types of myopathy are being included in this category Muscle biopsy usually reveals no definite abnormality and the electromyogram is often normal

Infantile muscular dystrophy and lipoid and glycogen storage diseases may also produce a clinical *picture of progressive atrophy and enfeeblement of* muscles The diagnosis of *glycogen storage disease* (von Gierkes disease) should be entertained when the syndrome of infantile muscular atrophy is associated with clinical enlargement of heart liver or spleen The motor disturbance in this condition may be related in some way to the abnormal deposits of glycogen found in skeletal muscle though it is more likely due to the degeneration of the anterior horn cells of the spinal cord which are distended with glycogen and other substances Lipoid storage disease of *Tay Sachs* and the variants which occur later in life may also cause thinness of limb musculature feebleness of movement and diminution or loss of tendon reflexes Regression of mental development blindness macular degeneration which are almost always present to some degree should leave little doubt as to the nature of the illness Also muscular dystrophy either familial or nonfamilial may begin during fetal life or during infancy and childhood There is obvious palsy of the limbs with proximal and trunk muscles more involved than distal ones Contractures are frequent with a leg or arm held in a curious ab

ganic driveness is perhaps more commonly observed in acquired postnatal encephalitis than with congenital diseases Rhythmic rocking rolling head banging and bouncing movements are common in retarded children and may be performed hour after hour often to the accompaniment of bleating sounds squeals and other ejaculations Here the abnormality is not the appearance of rhythmic movements of the body which are observed at one period in the development of many normal children but their persistence Music may encourage rhythmic movement and gives pleasure to many retarded children

The least severely retarded child (IQ 50 to 70) grows and develops in many ways not different from normal and he can be taught useful occupational skills A few can work under careful supervision

Special Varieties of Mental Retardation Several of the special types of mental retardation have already been discussed in this and other chapters (cf Lipoidoses and Cerebral Sclerosis in Chap 259) In the following pages are presented only those with special features

Mongolism This is a unique condition and although accounting for only about 1 per cent of all mental defectives it is the reason for one third to one half the admissions to state schools Mental retardation which varies from mild to severe a curious facial configuration with an Oriental cast to the eyes and a dwarfed physical stature constitute a clinical triad Many of the stigmas of mongolism can be recognized in the neonatal period The head tends to be small and oval with the forehead sloping The ears are set low on the scalp and are oval with small lobules The eyes slant slightly upward and outward owing to the presence of an epicanthal fold which covers the medial angle of the palpebral fissure The bridge of the nose is generally absent or poorly developed and the crest of the nose small The mouth tends to hang open and the tongue is usually enlarged heavily fissured and protruding Gray white specks of depigmentation are seen in the iris (Brushfield s spots) The little fingers are often short and curved owing to a hypoplastic middle phalanx The hands are broad and simianlike with a single transverse palmar crease Lenticular opacities and congenital heart lesions are found in some cases At birth the mongoloid child is of average size but at later periods of life he is characteristically small Benda estimates that the average adult person with mongolism of whom there are many never exceeds the stature of a ten year old boy The resemblance to the Oriental is at most superficial in fact the differences are so striking that it is quite easy to recognize the condition in those of Oriental heritage

The cause of mongolism is not known It has been suggested that the defects arise as a result of some metabolic abnormality which occurs late in the second or early third month of pregnancy Older mothers are more apt to have mongoloid babies than are young mothers The mean age of the mother at the time of birth of the mongoloid child is thirty seven It is thought by some workers that a genetic factor is responsible but familial incidence is rare Aside from a rather rounded brain which conforms to the shape of the skull a subnormal weight and a relatively simple convolutional pattern no abnormalities can be seen in the brain of the mongolian idiot Pituitary extracts of doubtful potency have been used in treatment but the results are impossible to evaluate

Cretinism This is due to congenital deficiency of thyroid secretion and is distinguished from myxedema a form of hypothyroidism acquired later in life It develops most often in areas where goiter is endemic The typical symptoms and signs are usually recognized between the sixth and twelfth months of life when retardation of growth and the curious alterations in physical appearance first appear The thick lips the puffy eyelids the short wrinkled forehead with low hair line the broad nose the open mouth with large protruding tongue the pale mucous membranes the dry skin and the coarse scanty hair comprise a highly distinctive picture Also it is to be noted that the body is small the limbs are short and there is a protuberant abdomen There are prominent fat pads above the clavicles in the axilla and between the shoulder blades The temperature tends to be subnormal and the pulse slow These findings usually distinguish the cretinoid from the mongoloid or gargoyloid child with whom he may be confused X rays are an additional aid for they show that the centers of ossification are delayed in their development The carpal and tarsal bones may not appear until the tenth year The tendon reflexes are of small amplitude and prolonged Intelligence is nearly always impaired Many cretins never learn to talk or at most may say only a few words Standing walking and all actions are retarded Their disposition is remarkably amiable In a few of the reported cases there has been cerebral diplegia The protein content of the cerebrospinal fluid is often elevated The pathologic anatomy of the brain disease is poorly described no thorough studies of it have been made In the authors material inadequate though it is no convincing histologic changes have been found Once cretinism has fully developed thyroid replacement is of no value A premium must therefore be placed on early diagnosis for thyroid replacement therapy during the first year of life may result in marked improvement Even then normal mentality may not be attained because it is said of an associated developmental abnormality of the brain

may affect the brain at an early age and prevent normal mental development It becomes necessary to acquire a way of thinking about these problems The authors bedside approach has been to attempt to categorize each case according to the scheme presented below This can be done by obtaining the necessary clinical data—a careful history in order to determine whether or not the condition is progressive and a physical examination in which one searches for evidences of cranial skeletal ectodermal cardiac and other developmental abnormalities Once a patient is categorized it is less difficult to decide which of several diseases is present

CLINICAL CLASSIFICATION OF THE VARIETIES OF NONPROGRESSIVE MENTAL RETARDATION

I Mental defect with associated developmental abnormalities in nonnervous structures
  - *A* Those affecting cranioskeletal structures
    1. Microcephaly
    2. Macroencephaly
    3. Hydrocephalus
    4. Craniostenosis
    5. Morquio s disease
    6. Gargoylism
    7. Mongolian idiocy
    8. Cretinism
    9. Cleidocranial dysostosis
    10. Achondroplasia
    11. Gonadal dysgenesis (Bonnaire Ullrich Turner syndrome)
  - *B* Those affecting nonskeletal structures
    1. Phakomatoses (tuberous sclerosis von Recklinghausen s disease Sturge Weber syndrome etc)
    2. Ectodermal dysplasia
    3. Congenital heart disease
    4. Deafness and congenital heart disease following maternal rubella

II Mental defect without developmental anomalies in nonnervous structures but with focal cerebral and other neurologic abnormalities
  - *A* Cerebral spastic diplegia with or without involuntary movements
  - *B* Cerebral hemiplegia unilateral or bilateral
  - *C* Congenital choreoathetosis or ataxia
    1. Kernicterus
    2. Status marmoratus (hypoxia?)
  - *D* Congenital atonic diplegia
  - *E* Rarely with other inherited neuromuscular abnormalities (muscular dystrophy Friedreich s ataxia etc)

III Mental defect without signs of other developmental abnormality or neurologic disorder
  - *A* Simple mental retardation
  - *B* Kernicterus
  - *C* Hypoxia
  - *D* Phenylpyruvic oligophrenia } These may be progressive
  - *E* Galactosemia }
  - *F* Heller s disease }

A number of progressive neurologic diseases—chronic subdural hematoma neurosyphilis toxoplasmosis lipoidoses and cerebral scleroses—may be confused with these static defects

Clinical Characteristics As an aid to the general physician who must undertake the diagnosis and management of backward children the following comments may be of some value Mental retardation manifests itself in the spheres of motor language social and intellectual development The severely retarded child at idiot level with an Intelligence Quotient (IQ) of less than 20 and unable to look after himself often does not sit up walk or stand and if any of these motor activities are acquired they appear late and are imperfectly performed Language is not mastered or at most only a few words are understood and uttered Physical growth is usually retarded nutrition may be poor and susceptibility to respiratory infections is common Sphincteric control is never accomplished Most of these severe aments never learn to dress bathe or feed themselves or to use implements and common tools Physical deformities are common in this group and they always suggest that the brain disease began in the antenatal period because of either a genetic disorder or a disease which occurred during the first 12 weeks of pregnancy Affections of the nervous system which have their onset later in life are usually not attended by bodily disfigurement

If the mental defect is less pronounced with the IQ 20 to 50 (i e imbecile) or 50 to 70 (i e moron) and if specific motor defects do not coexist then sitting walking and speech are acquired but only after a delay in many cases The existence of a cerebral defect may be noted for the first time when the child fails to speak normally during the second and third years of life and seems not to be able to learn the usual household tasks as well as other children However delay in language development must not by itself be taken as a mark of mental retardation for many bright children who are obviously intelligent and who show remarkable talent in communicating by gesture are slow in talking Toilet training also may be difficult to accomplish in the retarded child but again it may be delayed in an otherwise normal child because of incorrect parental attitudes and emotional problems The appearance of these retarded children is revealing for many have a dull apathetic appearance and their motor activity may be either reduced or excessive Some are very docile and affectionate others display a curious inquisitiveness irritability and destructiveness The most extreme degree of this overactivity is seen in the patient with "organic driveness a term introduced by Eugene Kahn to designate the incessantly moving incorrigible child who strikes at or bites every person or object which thwarts him in any way and who demolishes every object which he can reach Some of these children seem strangely impervious to injury and neither reward nor punishment influences them This or

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Gargoylism (Hunter Hurler Disease) A metabolic abnormality which affects the brain the cranial bones and skeleton and the internal organs (liver spleen heart lungs and blood) this disease appears in families apparently being determined by an autosomal recessive gene The symptoms and signs usually become manifest during the early years of life The appearance of the patient is most striking and will alone permit diagnosis The head is slightly enlarged dolichocephalic or scaphocephalic with rather shallow orbits and protruding eyes and forehead The bridge of the nose is depressed and the eyes widely spaced The lips are thick and the tongue seems too large for the mouth interfering somewhat with breathing Breathing is rather noisy as though the oropharynx and mouth were partially obstructed The cornea has a steamy or cloudy appearance Growth is stunted and most patients are dwarfs The neck and trunk are usually short and the vertebrae malformed A kyphotic deformity of the thoracic spine is a frequent finding The extremities are short and the hands and feet broad and spadelike Many of the joints are ankylosed The abdomen protrudes to allow room for the enlarged liver Mental development may be normal or retarded to a variable degree Hydrocephalus may occur Granules of a material that takes a glycogen stain have been seen in neutrophilic leukocytes in the circulating blood Postmortem examination has shown the nerve cells to be swollen with inclusion material which chemical analysis shows to be a ganglioside like that found in the nerve cells of Tay Sachs infantile Gaucher s and Niemann Pick diseases There are also fat laden macrophages in the perivascular spaces and in the meninges both macrophages and an increase in fibrous tissue Glycogen and a peculiar lipoprotein material are also found in liver cells and the Kupffer cells and macrophages in a fashion reminiscent of von Gierke s disease The skeletal abnormality is said to be an osteochondrodystrophy The disease is progressive and fatal within a few years in most instances There is no treatment

Osteochondrodystrophy (Morquio s Disease) Sometimes confused with gargoylism this is a nonprogressive osseous disorder with a cranial appearance similar to that of gargoylism Some patients have a normal mind others have a stationary mental defect but in the latter none of the typical brain lesions of gargoylism have been found and the nature of the anatomic defect remains unknown No visceral lesions have been observed The primary defect is believed to be one of the chondroblasts

Phenylketonuria (Phenylpyruvic Oligophrenia) This condition is discussed in Chap 92 Disorders of Amino Acid Metabolism to which the reader is referred for the biochemical findings Jervis has estimated that 1 in 25 000 people in the United States has the disease It has been observed in individuals of Mediterranean Scandinavian and Irish origin and has seldom been seen in Jews and Negroes Characteristically the affected person is of light complexion with blue eyes but a few have been of darker complexion The lightness of complexion is thought to be due to a defect in pigment metabolism Those with the lighter coloring are said to have a lower intelligence Some patients are of small stature and the circumference of the head may be subnormal The mental defect is generally not recognized for some months or years after birth and appears to be progressive The degree of retardation varies from mild to severe Seizures occur in approximately 20 per cent of cases There are usually no associated neurologic symptoms and signs There are no consistent histopathologic changes in the brains of uncomplicated cases If the diagnosis is made early the administration of a diet low in phenylalanine is said to have resulted in clinical improvement

Galactosemia Another congenital metabolic disease galactosemia is thought to be transmitted by a single autosomal recessive gene It is characterized clinically by mental defect cataract nausea vomiting hepatomegaly jaundice and the excretion of large quantities of galactose in the urine The biochemical defect is discussed in Chap 94 The manner in which galactosemia induces the symptoms and signs of the neurologic disorder is not known No pathologic studies are available The infants are normal at birth but on the usual milk diet develop signs of malnutrition nausea and vomiting Soon the other symptoms develop The diagnosis should be suspected whenever reducing substances are present in the urine of retarded children There are however no ketone bodies and acidosis does not occur Galactose can be identified by paper chromatography or by the formation of a specific osazone Aminoaciduria and abnormally flat glucose tolerance curves are helpful diagnostic laboratory findings Hypoglycemia may be found and aggravated temporarily by the injection of galactose Replacement of milk in the diet with its high content of galactose is said to result in clinical improvement

Anhidrotic Ectodermal Dysplasia This is a congenital disorder in which there are anhidrosis defects in salivation lacrimation sparse hair and faulty dentition Heat intolerance with paroxysmal fever unrelated to infection may occur Several of the reported cases have been feebleminded A sex linked inheritance pattern has been reported The neuropathologic basis for this disease is unknown There is no treatment

Heller s Disease (Dementia Infantilis) This condition is of uncertain status Neurologists and some

psychiatrists look upon it as a cerebral disease of undetermined cause Other psychiatrists believe it to be a form of precocious schizophrenia As a rule the onset is in about the third or fourth year of life At this age usually without previous illness a change in character is noted Irritability negativism disobedience and outbursts of unprovoked temper become manifest Restlessness and destructiveness are other prominent symptoms Toys with which the child had played normally are now senselessly destroyed Within a few months there is complete loss of speech and also failure in the understanding of words Grimacing and ticlike movements appear but motor and sensory functions are preserved Continence of sphincters is lost The mental regression continues to a stage of idiocy but all through the illness the patient continues to give an impression of greater intelligence than do most feebleminded individuals Many patients of this type reach adult life but remain in institutions The pathology of the disease is unknown A few of the reports state the brain to be abnormal and suggest that there may be degeneration of ganglion cells like that of Tay Sachs disease but the illustrations are unconvincing There is no treatment The relationship of this disease to many cases of so called childhood schizophrenia" is not always clear It is said that the patient with childhood schizophrenia although withdrawn and mute maintains an inquisitive interest in his surroundings and is clever in handling tools and in manipulating objects

Simple Mental Retardation Although presented last this category includes the great bulk of children with mental defect of indeterminate etiology who exhibit neither craniovertebral nor neurologic abnormality The degree of mental impairment tends to be mild (moron feebleminded educable) or moderate (imbecile trainable) Penrose found that this group of aments comprised 24 per cent of 1 280 institutionalized children and of course those who are in institutions represent only the more severely damaged individuals in our society The physical appearance of these children is usually not strikingly abnormal yet many of the afore mentioned characteristics of the mentally retarded child are to be observed Seizures occur in a significant number being several times more frequent than in a normal population Within the limits of their intelligence the success of these children in learning to look after themselves is often determined by the effectiveness of their teachers and the suitability of the environment in which they are placed The brighter ones can profit to some extent from formal education Those less well endowed may be trained to care for their personal wants and needs and may profit from a limited amount of manual training Special schools and classes are of great help

Society in the final analysis determines the eventual disposition of these unfortunates Many of them being not unattractive and giving less trouble than many other defective children may adjust to foster families and live in a community They need protection for they are easily led astray and may commit infractions of the law usually of a minor sort Sexual offenses are common in the girls Institutionalization is required when family and society cannot or do not wish to look after them Reproductivity is frequently impaired in those with severe mental defect but may be distressingly undisturbed in many of the less defective individuals

The problem of eugenics assumes great importance This type of mental defect is often seen in families where one or both parents are dull or retarded The term *familial* may be applied to this group However the majority of cases are sporadic Probably there are multiple etiologic factors which may lead to simple mental retardation The pathology is variable ranging from "no demonstrable lesion" to several different gross and microscopic abnormalities

Management of the Retarded Child and His Parents It is an unpleasant task to inform parents that their child is abnormal in any respect and many if not most parents find it difficult to accept a mental defect without much self recrimination and feeling of guilt To give an honest statement of the degree of the child s retardation and based on the nature of the problem some professional estimate of the likelihood of future growth and development once one is sure of the status and potentialities of the child requires tact and sympathetic understanding The family must eventually be told to what extent the child is likely to be trainable or educable Obviously this can often be no more than an educated guess and if there is still reasonable doubt about the future this fact should be so stated In general it should be possible to give at least a rough approximation of the child s capabilities and likely attainments Frequently the parents themselves are well aware of the child s limitations and then a useful technique is to ask the parents to estimate the nature of the problem The physician is in this way informed of the degree of their insight and their general attitudes He may then agree with them or may amplify and clarify any misconceptions

The parents will want to know the probable cause of the defect and the likelihood of subsequent children being affected In most instances the answer to the second question will depend on the etiology If the abnormality is determined by known genetic factors as in congenital microcephaly phenylpyruvic oligophrenia or tuberous sclerosis there is of course a strong likelihood of other children being abnormal If on the other hand the abnor

mality is due to specific environmental influences peculiar to the pregnancy as in the case of maternal rubella or excessive radiation to the pelvis the prospects of having other normal children are good Unfortunately in the great majority of cases the etiology will not be clear and advice must be tendered cautiously It is quite clear from the studies of Penrose Halperin and others that the chance of parents of normal intelligence with one defective child having other subnormal children is greater than that of the general population If one or both parents is of less than normal intelligence or if there is consanguinity in the parents then the risk is considerably greater A recessive trait in a first child which is inherited in only one of four children and cannot be passed on in overt form to succeeding generations need not discourage a family from "taking a chance on having other normal children

Special Paroxysmal Disorders of Nervous Function in Infancy and Childhood

The convulsive disorders have been discussed in Chap 35 *Recurrent Convulsions* and all that was said there applies to infants and children as well as adults There are however many special problems raised by the child who is having spells or seizures and these must be known and properly interpreted by the physician who upon seeing the patient at a more advanced age obtains the history of these spells

The incidence of convulsions is known to be high in infancy and early childhood and seizures at that age may have an altogether different significance than in the adult All the seizure patterns that may be witnessed in the adult may also occur in infancy and childhood—i e focal motor and Jacksonian as well as petit mal and psychomotor seizures—but certain ones appear at this age which are not often observed in the adult These are the petit mal and its variants and massive myoclonus Then too there are other types of spells unique to infancy and childhood which must be distinguished from convulsions i e breath holding spells and the congestive attacks that accompany congenital heart disease

Seizures have different meanings at different periods of infancy and childhood A series of seizures that occurred during the neonatal period must always be regarded as an omen of cerebral damage It may have been due to subdural and subarachnoid hemorrhage in which unresponsiveness pallor periods of apnea bulging fontanel and grossly bloody cerebrospinal fluid clarify the diagnostic problem It may reflect a congenital brain disease sometimes of such major proportions as to have prevented further development or it may have been so slight as not to disturb the normal maturation processes Actually very little is known of the import of seizures at this period with reference to prognosis for mental development Infantile tetany during the first 2 to 3 weeks of life may have been the cause of seizures as well as of a remarkable stiffness of limbs and carpal spasms (The Chvostek sign is misleading at this age being present in many normal babies) Only the blood calcium and phosphorus levels and the response to intravenous calcium would have confirmed the diagnosis A single outburst of seizures in a previously healthy infant may have been merely an expression of the low convulsive threshold of the infantile nervous system as in febrile convulsions or may signify a mortal process such as the water intoxication syndrome acute toxic encephalopathy thrombosis of the superior sagittal sinus or cerebral veins meningitis hypoglycemia brain hemorrhage from an angioma or massive arterial infarction Idiopathic epilepsy also begins during infancy and childhood and may interfere relatively little with normal development Brain tumors are an infrequent cause of seizures during infancy and childhood

Febrile Fits

Certain infants and children are disposed to convulsions with fever Lennox estimates that approximately 2 per cent of all children have one or more convulsions with fever at one time or another during infancy or childhood In some 20 per cent of these cases it can be decided in retrospect that fever has served merely to precipitate a seizure in an individual who has suffered a cerebral disease or who has idiopathic epilepsy Such individuals will continue to have seizures unassociated with fever In the other 80 per cent of cases seizures occur only during febrile episodes and never recur beyond early childhood The reason for this low seizure threshold in the infantile brain is unknown but a family history of similar febrile fits in other members of the family can be obtained in about 50 per cent of cases

From the history it can usually be learned that febrile convulsions have occurred between the ages of one and three years only a few cases are seen earlier or later—up until the age of seven or eight years Any febrile illness may have been provocative but usually a rapid ascent of temperature to 103 F or higher was responsible The seizures themselves are generalized and of short duration and may have occurred singly or in a cluster of two or three The postictal coma is of short duration No record of focal or lateralizing neurologic signs can be obtained The cerebrospinal fluid is clear and acellular and the total protein normal The EEG is diffusely abnormal with theta and delta waves predominating in all leads immediately after the seizure with rapid return to normal at

the termination of the illness After the illness there should be no residual signs of brain disease

It must be remembered that there are certain sources of error in the diagnosis of febrile convulsions The fever may have been caused by convulsions as so often happens in idiopathic epilepsy especially with status epilepticus Some primary inflammatory disease of the brain or meninges may have been responsible for both fever and convulsions Meningitis for example may have begun in this way but would probably have ended fatally if not diagnosed and treated

Massive Myoclonus

This syndrome known also by the names *infantile muscular spasm Blitzkrampf myoclonic seizure* Salaam fit" flexor spasm and "jackknife seizure has been recognized recently and should be known to general physicians and internists for they may see the patient long after the seizures have stopped In essence it is a sudden synchronous contraction of many muscle groups Contraction of flexor muscles usually predominates and there is a sudden flexion of trunk neck and extremities often accompanied by a cry or occasionally by a laugh In some patients there is a combination of flexor and extensor movements and least often the contraction of extensor muscles predominates with a straightening of the body and a fall backwards The spasm itself is usually momentary but often recurs one or several times with each spasm separated from the next by an interval of a few seconds There may be only a few spasms in a cluster or upwards of a hundred or more in a series They are especially frequent as the patient is falling off to sleep or upon awakening The patient may fall if he is standing at the time of the spasm Sensory precipitation by handling feeding noise and fever have been noted

Massive myoclonic spasms usually begin during the first few months of life and tend to disappear or to be replaced by other seizure patterns between the second and third years of age The pathophysiology is not well understood and the neuropathology of the condition has not been studied systematically The frequent association of mental retardation (over half the cases) and the consistent diffusely abnormal electroencephalogram with bursts of high voltage slow waves referred to as *hypsarrhythmia* by Gibbs suggest a diffuse neuronal pathology It is of interest that the seizures may become less frequent as the dementia progresses

In early life parents may mistake the flexor spasm for colic This is especially true when feeding is a precipitating stimulus Colic however is never associated with even a transient loss of consciousness Associated seizure phenomena such as rolling up of the eyes and pupillary dilatation may be helpful points In the young infant this condition may also be confused with the Moro reflex but such an error is avoided if one gives attention to the precipitating sensory stimulus which is different in the two conditions and to the movements which usually occur in series Nevertheless the similarity of the movement pattern suggests that massive myoclonus and the Moro response probably both *utilize the same physiologic mechanisms*

The treatment of the seizures is difficult Some respond dramatically to the first drug tried but soon become resistant to it Diamox alone or in combination with phenobarbital has proved to be the most useful drug in the authors experience

"Breath holding Spells"

This is a special type of attack peculiar to young children and should have no significance in later life unless it becomes the basis of a psychologic problem Anger or a mild injury is the precipitating factor The patient begins to cry or scream After a few moments he suddenly stops breathing and remains apneic for many seconds to as long as a minute During this period there is a color change from an initial redness to cyanosis presumably as the result of hypoxia If this persists for a short period the patient suddenly becomes limp and is unresponsive for some seconds Convulsive twitching may occur but rarely is there a sustained convulsion The whole attack is over in from one to a few minutes The child may then be drowsy and sleep for a short while thereafter or may be at once as alert as before Such attacks usually begin late in the first year of life and rarely after the third year They are outgrown so to speak The mechanism is unclear in breath holding the infant may perform the Valsalva maneuver and then faint as in tussive syncope The treatment consists of reassurance and a careful explanation of the spells to the family It should be pointed out that in certain instances a child may seem to use" the attacks to obtain what he wishes and that by ignoring them they may be eliminated or reduced in number

Apnea may be observed as a fragment of a generalized seizure and must be differentiated from breath holding The sequence of events is so characteristic in breath holding that the diagnosis is usually not difficult

Congestive Attacks with Congenital Cardiac and Pulmonary Disease

This condition has been described only recently and is of importance in the histories of cases of congenital heart disease Cyanotic infants and children with gravely limited cardiopulmonary function may upon some unusual exertion or excitement or while crying momentarily lose consciousness and twitch a few times Presumably the spell depends

on hypoxia or inadequacy of cerebral blood flow It must be distinguished from seizures which occur with a higher than normal frequency in patients with congenital heart disease

Hypoglycemia

As stated in Chap 33 Coma and Related Disturbances of Consciousness hypoglycemia may cause seizures and unresponsiveness but as a rule the seizure does not interrupt a normal state of consciousness An unexpected convulsion is almost never due to hypoglycemia alone When this state is encountered in infants it is sometimes traceable to a hepatic form of glycogen storage disease in which there is an inherited defect of an enzyme system necessary in the synthesis or breakdown of glycogen These children tend to be obese Hepatomegaly and splenomegaly are important clinical features The failure of epinephrine to produce a significant rise in the blood sugar levels is diagnostic of glycogen storage disease Treatment consists of a regular diet supplemented by carbohydrate about 45 min after each meal to offset the fall in blood sugar

Older children are prone to attacks of idiopathic hypoglycemia They tend to be thin rather than obese and the attacks occur on a background of relatively poor intake of food or actual fasting for 12 to 36 hr Occasionally the child has engaged in unusually strenuous and prolonged exercise prior to an attack The mechanism is not clearly understood but depletion of glycogen stores and lack of available sugar due to fasting have been suggested The symptomatology is fairly characteristic The child is noted to be apathetic or mentally dull and pale Vomiting occurs early and there may be a complaint of hunger despite the vomiting If no food is ingested stupor coma or convulsions may develop The seizures tend to consist of irregular poorly synchronized twitchings that may shift from side to side They may continue for long periods A well circumscribed isolated convulsion however is uncommon

Hypoglycemia as a result of hypopituitarism Addison s disease and renal glycosuria as in the de Toni Fanconi syndrome is occasionally seen in children Pancreatic adenomas are rare in this age group

CONCLUSION

A knowledge of these special neurologic problems of infancy and childhood is of value to the student as well as to the general physician or internist it enables him to understand the nature of such illnesses when they are encountered in adults and permits better evaluation of their role in any new illness Also the habit of making observations on the level of native intellectual endowment is of importance The histories given by patients with neurologic problems must always be carefully checked against an outside source in planning for therapy one must always enlist the aid of the responsible member of the family or if the patient is institutionalized of the nurse or attendant Finally problems in eugenics are likely to arise and the physician is often asked to advise the family or health agencies in the community on such matters Accurate diagnosis and a carefully established genealogy usually permit a separation of a genetic from an acquired disease and are of some value in predicting the occurrence of such diseases in the progeny of the afflicted individual

REFERENCE

Ford F R Diseases of the Nervous System in Infancy Childhood and Adolescence 3d ed Springfield Ill Charles C Thomas Publisher 1952

254 CEREBROVASCULAR DISEASES

C Miller Fisher, Herbert R Karp and Raymond D Adams

Vascular diseases of the nervous system rank first among all the diseases of the nervous system The recognition of this fact and of the need of careful investigation of the causes and mechanisms of these diseases has aroused increasing interest in this subject in the past few years and for the first time the common stroke case is being made the object of systematic study Furthermore it is evident to all who work in this field of medicine that the cerebrovascular diseases provide one of the best approaches to the study of neurology No other group of diseases creates with such precision a localized brain lesion of comprehensible type and permits a nervous disorder to unfold with such clarity In past times the neurologist in attempting to learn the secrets of the function of the human brain has depended heavily on the focal ischemic lesion and there is no reason to doubt that cerebrovascular diseases will continue to offer instructive examples of disorders of nervous function the assiduous study of which will be well repaid

Every neurologic disease may be said to involve the vasculature of the nervous system in one way or another and it is necessary at the very outset to delineate the boundaries of the subject The term *cerebrovascular disease* is intended here to denote any disease in which one or more of the blood

vessels of the brain is primarily implicated in a pathologic process By pathologic process is meant any abnormality of the vessel wall an occlusion by thrombus or embolus rupture of a vessel a failure of cerebral blood flow due to a fall in blood pressure a change in the caliber of the lumen altered permeability of the vascular wall or increased viscosity of the blood The pathologic process within the vessel can be described not only according to its grosser aspects—thrombosis embolism rupture of a vessel etc —but also in terms of the more basic vascular disorder i e atherosclerosis hypertensive arteriolosclerosis arteritis trauma aneurysm developmental malformation etc Furthermore in classifying cerebrovascular diseases it is not sufficient to consider only the primary vascular lesion but equal weight must be given the resulting parenchymal changes The e pathologic effects in the brain are of two types ischemia with or without infarction and hemorrhage Aside from these the vascular lesion is silent the only exceptions being the local pressure effects of an aneurysm vascular headache (migraine hypertension arteritis) and occasionally increased intracranial pressure as in hypertensive encephalopathy and venous thrombosis

CLASSIFICATION

The following classification[1] is somewhat unorthodox and requires a few words of explanation First, in order to give the student an idea of the scope of this field the classification includes all the cerebrovascular diseases listed chiefly according to the parenchymal changes but also when indicated according to the primary vascular changes The common diseases and the common pathologic conditions are indicated in heavy type in order that they will not be lost among relatively rare or less important conditions Secondly this arrangement traces the steps followed by the clinician in reaching a clinical diagnosis in other words it outlines the clinical approach Lastly the classification is intended to serve the pathologist who also proceeds in his investigations by first determining the nature of the parenchymal lesion i e infarction or hemorrhage and then by seeking evidence of the underlying vascular disorder

It will be seen that there are nine major categories I Cerebral Infarction II Transient Cerebral Ischemia without Infarction III Intracranial Hemorrhage IV Vascular Malformations V The Arteritides VI Hypertensive Encephalopathy VII Dural Sinus and Cerebral Vein Thrombosis VIII Strokes of Undetermined Origin and IX Vascular Diseases without Changes in the Brain

Four principal conditions account for the majority of cerebrovascular lesions cerebral infarction due to atherosclerotic thrombosis (40 per cent) cerebral infarction due to embolism (25 per cent) hypertensive intracerebral hemorrhage (20 per cent) and ruptured saccular aneurysm or angioma (8 per cent) These four conditions occupy prominent places under Infarction (I) and Hemorrhage (III) Cerebral Ischemia without Infarction is given a separate nosologic position because of its clinical importance and therapeutic implications Vascular Malformations (IV) the Arteritides (V) and Venous Thrombosis (VII) are diagnostic entities of such distinctive attributes as to merit separate classification Hypertensive Encephalopathy (VI) represents a unique pathologic process and warrants a separate niche Strokes of Undetermined Origin (VIII) and a list of the Primary Vascular Diseases (IX) complete the classification

- I Cerebral infarction (pale red (hemorrhagic) and mixed types)
  - A Thrombosis with atherosclerosis
  - B Embolism
    - 1 Cardiac origin
      - a Atrial fibrillation and other arrhythmias (with rheumatic atherosclerotic hypertensive congenital heart disease)
      - b Myocardial infarction with mural thrombus
      - c Acute and subacute bacterial endocarditis
      - d Heart disease without arrhythmia or mural thrombus (mitral stenosis, etc)
      - e Complications of cardiac surgery
      - f Nonbacterial thrombotic ("marantic") endocardial vegetations
      - g Paradoxic embolism with congenital heart disease
    - 2 Noncardiac origin
      - a Atherosclerosis of aorta and carotid arteries (mural thrombus atheromatous material)
      - b From sites of cerebral artery thrombosis
      - c Thrombus in pulmonary veins
      - d Fat
      - e Tumor
      - f Air
      - g Complications of neck and thoracic surgery
      - h Miscellaneous rare types
      - i Of undetermined origin
  - C Other conditions causing cerebral infarction
    - 1 Ruptured saccular aneurysm

[1] This classification was drawn up by an ad hoc committee of the National Institute of Neurological Diseases and Blindness and will be included in the Transactions of the Second Princeton Conference on Cerebral Vascular Diseases to be published for the American Heart Association by Grune & Stratton in 1958

[2] These data are the result of a neuropathologic study by one of us (CMF) of 4x2 unselected autopsies

2 Cerebral venous thrombosis
3 Systemic hypotension
4 Complications of arteriography
5 Arteritis (see V)
6 Hematologic disease (polycythemia sickle cell disease thrombotic thrombopenia etc)
7 Dissecting aortic aneurysm
8 Trauma to carotid
9 Hypoxia
10 Radioactive or x ray radiation
11 With tentorial foramen magnum and subfalcial herniations
12 Miscellaneous rare types (e g migraine)

D Cerebral infarction of undetermined cause

II Transient cerebral ischemia without infarction

A Recurrent cerebral ischemic attacks (previously called vasospasm usually associated with atherosclerosis and thrombosis)

B Systemic hypotension (i e simple faint acute blood loss myocardial infarction Stokes Adams syndrome traumatic and surgical shock sensitive carotid sinus severe postural hypotension)

1 With focal neurologic deficit
2 With syncope

C Migraine

III Intracranial hemorrhage (including intracerebral subarachnoid and ventricular rarely subdural)

A Hypertensive intracerebral hemorrhage
B Ruptured saccular aneurysm (if unruptured see IV*A*)
C Angioma (if unruptured see IV*B*)
D Trauma
E Hemorrhagic disorders (leukemia aplastic anemia thrombopenic purpura liver disease complication of anticoagulant therapy hyperfibrinolysis etc)
F Hemorrhage of undetermined cause (normal blood pressure and no angioma)
G Hemorrhage into primary and secondary brain tumors
H Septic embolism mycotic aneurysm
I With hemorrhagic infarction arterial or venous (see under I and VII)
J Secondary brain stem hemorrhage (temporal lobe herniation)
K Hypertensive encephalopathy
L Idiopathic brain purpura
M With inflammatory disease of arteries and veins (see under V VII)
N Miscellaneous rare types

IV Vascular malformations and developmental abnormalities

A Aneurysm—saccular fusiform globular diffuse (if ruptured see III*B*)
B Angioma [including familial telangiectasia trigeminal encephaloangiomatosis of Sturge Weber Dimitri and retinal pontine hemangiomas (if ruptured see III*C*)]
C Absence hypoplasia or other abnormality of vessels (including variations in pattern of circle of Willis)

V Inflammatory diseases of arteries

A Infections and infestations

1 Meningovascular syphilis
2 Septic embolism
3 Arteritis secondary to pyogenic and tuberculous meningitis
4 Rare types (i e typhus schistosomiasis mansoni malaria(?) trichinosis(?) etc)

B Diseases of undetermined cause

1 Lupus erythematosus
2 Polyarteritis nodosa (necrotizing and granulomatous forms)
3 Cranial (temporal) arteritis
4 Idiopathic granulomatous arteritis of aorta and its major branches

VI Hypertensive encephalopathy

A Malignant hypertension (essential chronic renal disease pheochromocytoma etc)
B Acute glomerulonephritis
C Eclampsia

VII Dural sinus and cerebral vein thrombosis

A Secondary to infection of ear paranasal sinus face or other cranial structures
B With meningitis and subdural empyema
C Debilitating states (marantic)
D Post partum
E Postoperative
F Hematologic disease (polycythemia sickle cell disease)
G Cardiac failure and congestive heart disease
H Miscellaneous rare types
I Of undetermined cause

VIII Strokes of undetermined origin

IX Vascular diseases without changes in the brain

A Atherosclerosis
B Hypertensive arterio and arteriolosclerosis
C Hyaline arterio and arteriolosclerosis
D Calcification and ferruginization of vessels
E Capillary sclerosis etc

GENERAL ASPECTS

The Cerebrovascular Stroke as a Clinical Phenomenon The clinical picture resulting from vascular disease is in most instances so distinctive that the diagnosis is more readily made than any other in the realm of neurology The cardinal feature is the *stroke* a term which connotes the sudden and dramatic development of a focal neurologic deficit In the severest form of a stroke the patient falls unconscious and inert with evidence of hemiplegia—an event so striking as to deserve its own separate designation viz apoplexy stroke shock or cerebrovascular accident In its mildest form it may consist of only a trivial neurologic disorder insufficient to disturb the customary activities of the patient or to demand medical attention

Undoubtedly the most characteristic feature is

the sequence of events which may be called the *temporal profile* of the stroke It is the suddenness of onset that especially stamps the disorder as vascular The speed of evolution though variable depending on the cause is rapid and the deficit may require only seconds minutes hours or at most a few days to develop When the stroke develops over a period of several days it usually progresses in a stepwise fashion i e in a series of sudden changes rather than smoothly A slow gradual downhill course over a period of days or weeks indicates that the process is probably not vascular in nature Later in the course of the illness if the attack is not fatal some degree of stabilization and then recovery occurs Not infrequently an extensive deficit reverses itself dramatically within a few hours or a day More often however the improvement is gradual taking place over weeks and months

It must not be supposed that every neurologic abnormality in patients with cerebrovascular disease can be related by the patient or his family to a stroke Often the exact date of onset of a given symptom cannot be remembered One has the impression that some of the vascular incidents especially in the hypertensive patient are so mild that they do not attract notice until their cumulative effects become manifest as a neurologic deficit of indeterminate date Furthermore patients with lesions in the right (nondominant) parietal region and anosognosia often cannot be depended upon to give any of the important details of their illness

The neurologic deficit in a stroke depends of course on the location of the infarct or hemorrhage in the brain and the size of the lesion Hemiplegia is the classical sign of vascular disease and occurs chiefly with massive lesions of either cerebral hemisphere but also with lesions of the brain stem In the most serious cases of hemorrhage the patient literally falls in his tracks paralyzed on one side and soon passes into deep coma and dies within a few hours In other cases more commonly in infarction the patient although hemiplegic remains alert and from the beginning it is obvious that he will survive his illness whether or not neurologic recovery occurs A stroke however may give rise to many manifestations other than a hemiplegia e g numbness sensory deficit dysphasia blindness double vision dizziness dysarthria etc In the following paragraphs these manifestations will be emphasized equally with hemiplegia

To summarize briefly it might be said that the stroke is the common denominator of all cerebrovascular disease and is recognized chiefly by its temporal profile and characteristic focal neurologic deficit

In practice however the diagnosis of cerebrovascular disease is established by the entire constellation of clinical features Often the patient is elderly and arterial hypertension is present There may be evidence of vascular disease at other sites e g heart lower limbs and aorta or the patient may have diabetes mellitus and thereby be predisposed to atherosclerosis A source of emboli may be present (auricular fibrillation myocardial infarction subacute bacterial endocarditis etc) Many strokes are preceded by transient warning episodes of weakness numbness dizziness etc and these attacks if they are nonconvulsive in nature should always suggest thrombotic cerebrovascular disease The neurologic signs may occur in certain combinations having a neurovascular relationship i e they may depend on structures which lie within a given vascular territory as in the lateral medullary syndrome and thus suggest occlusive vascular disease And last but not least the presence of blood in the cerebrospinal fluid signifies that the process is vascular and diagnostic deductions can proceed from that vantage point

CEREBRAL THROMBOSIS WITH ATHEROSCLEROSIS

Atherosclerosis in the arteries of the brain is similar to that elsewhere in the body The atheromatous plaques tend to form at branchings and curves The severity of the process runs parallel to that of other arteries aorta lower limbs and heart Thrombosis is most likely to occur where the plaque narrows the lumen to the greatest degree The commonest sites of thrombosis are the internal carotid artery at the carotid sinus in the neck and at the siphon intracranially at the main bifurcation of the middle cerebral artery in the region of the vertebral basilar junction in the posterior cerebral artery as it winds round the cerebral peduncle and in the anterior cerebral artery as it curves upward over the corpus callosum Hypertension aggravates the process and leads to deposition of atheromatous material in smaller vessels (1 mm and less) and thrombosis will then occur in the penetrating branches of the middle posterior cerebral and basilar arteries producing small infarcts called *lacunes* in the deeper parts of the basal ganglions and brain stem The details of the process by which thrombosis becomes superimposed on atherosclerosis are poorly understood It is a fairly reliable rule that when the systemic blood pressure is maintained atherosclerosis by itself is asymptomatic to lead to symptoms it must be combined with thrombosis unless hypotension occurs

The effect of atherosclerotic thrombosis on the brain is not easy to predict accurately and this is also true of embolic occlusion If the obstruction lies proximal to the circle of Willis collateral flow via the circle may be and often is adequate to

2 Cerebral venous thrombosis
3 Systemic hypotension
4 Complications of arteriography
5 Arteritis (see V)
6 Hematologic disease (polycythemia sickle cell disease thrombotic thrombopenia etc)
7 Dissecting aortic aneurysm
8 Trauma to carotid
9 Hypoxia
10 Radioactive or x ray radiation
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12 Miscellaneous rare types (e g migraine)

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A Hypertensive intracerebral hemorrhage
B Ruptured saccular aneurysm (if unruptured see IVA)
C Angioma (if unruptured see IV*B*)
D Trauma
E Hemorrhagic disorders (leukemia aplastic anemia thrombopenic purpura liver disease complication of anticoagulant therapy hyperfibrinolysis etc)
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K Hypertensive encephalopathy
L Idiopathic brain purpura
M With inflammatory disease of arteries and veins (see under V VII)
N Miscellaneous rare types

IV Vascular malformations and developmental abnormalities
A Aneurysm—saccular fusiform globular diffuse (if ruptured see III*B*)
B Angioma [including familial telangiectasia trigeminal encephaloangiomatosis of Sturge Weber Dimitri and retinal pontine hemangiomas (if ruptured see IIIC)]
C Absence hypoplasia or other abnormality of vessels (including variations in pattern of circle of Willis)

V Inflammatory diseases of arteries
A Infections and infestations
1 Meningovascular syphilis
2 Septic embolism
3 Arteritis secondary to pyogenic and tuberculous meningitis
4 Rare types (i e typhus schistosomiasis mansoni malaria(?) trichinosis(?) etc)
B Diseases of undetermined cause
1 Lupus erythematosus
2 Polyarteritis nodosa (necrotizing and granulomatous forms)
3 Cranial (temporal) arteritis
4 Idiopathic granulomatous arteritis of aorta and its major branches

VI Hypertensive encephalopathy
A Malignant hypertension (essential chronic renal disease pheochromocytoma etc)
B Acute glomerulonephritis
C Eclampsia

VII Dural sinus and cerebral vein thrombosis
A Secondary to infection of ear paranasal sinus face or other cranial structures
B With meningitis and subdural empyema
C Debilitating states (marantic)
D Post partum
E Postoperative
F Hematologic disease (polycythemia sickle cell disease)
G Cardiac failure and congestive heart disease
H Miscellaneous rare types
I Of undetermined cause

VIII Strokes of undetermined origin

IX Vascular diseases without changes in the brain
A Atherosclerosis
B Hypertensive arterio and arteriolosclerosis
C Hyaline arterio and arteriolosclerosis
D Calcification and ferruginization of vessels
E Capillary sclerosis etc

GENERAL ASPECTS

The Cerebrovascular Stroke as a Clinical Phenomenon The clinical picture resulting from vascular disease is in most instances so distinctive that the diagnosis is more readily made than any other in the realm of neurology The cardinal feature is the stroke a term which connotes the sudden and dramatic development of a focal neurologic deficit In the severest form of a stroke the patient falls unconscious and inert with evidence of hemiplegia —an event so striking as to deserve its own separate designation viz apoplexy stroke shock or cerebrovascular accident In its mildest form it may consist of only a trivial neurologic disorder insufficient to disturb the customary activities of the patient or to demand medical attention

Undoubtedly the most characteristic feature is

common Often there is evidence of vascular disease elsewhere e g angina pectoris electrocardiographic abnormality myocardial infarction absence of peripheral pulses in the lower limbs or intermittent claudication The retinal arteries may show uniform or focal narrowing increase and irregularity of the light reflex or displacement of the veins but these alterations cannot be correlated with cerebral atherosclerosis and thus fundoscopic examination is at present of little or no help in assessing the state of the intracranial arteries

The *specific neurologic abnormality* depends of course on the location and size of the infarct or the focus of ischemia The territory of any vessel may be affected large or small deep or superficial The carotid and basilar systems are approximately equally affected In involvement of the carotid system unilateral signs predominate hemiplegia hemihypesthesia hemianopia aphasia and agnosia In the basilar system hemiplegia may also be found but more commonly involvement here results in the occurrence of *bilateral* signs motor and/or sensory in combination with a disturbance of cranial nerves cerebellum or other structures localized in or related to the brain stem In order for carotid occlusion to cause bilateral signs the vessels to both hemispheres would have to be affected at the same time and this is uncommon (bilateral carotid occlusion) Therefore in identifying vascular syndromes it is important to determine if the signs and symptoms indicate unilateral or bilateral lesions

In order to understand the particular groupings of neurologic symptoms and signs the student must be familiar with certain points of neurovascular anatomy which will now be presented The clinical picture associated with occlusion of each of the cerebral and cerebellar arteries will then be understandable It must be remembered that because of the differences in collateral blood flow speed of occlusion etc the effect of occlusion at any one site is highly variable and therefore partial syndromes and minor modifications are extremely common indeed they are in the majority The following descriptions apply to infarction and ischemia due to thrombosis or embolism While hemorrhage in the same sites may give rise to many of the same effects nevertheless the total clinical picture is apt to differ because in its deep extension the hemorrhage may involve the territory of more than one vessel Also it displaces tissues and causes an increase in intracranial pressure

Vascular Ischemic Syndromes *Middle Cerebral Artery* The middle cerebral artery through its cortical branches supplies the lateral surface of the hemisphere except for the frontal pole a strip along the superomedial border supplied by the anterior cerebral and the lowermost temporal convolution, which is supplied by the posterior cerebral artery

Table 131 DEVELOPMENT OF THE CLINICAL PICTURE IN 125 CASES OF CEREBRAL THROMBOSIS

Clinical development	No of cases	Percentage
1 Stroke developing as a single event	21	17
a Abrupt (hours) with or without fluctuations	*14*	
b Slow gradual (several days) with or without minor fluctuations	*7*	
2 Stepwise development of a stroke with or without transient ischemic attacks	23	18
3 Transient ischemic attacks progressing to a persistent neurologic deficit major or minor	53	42
4 Development of a limited stroke followed by transient ischemic attacks	11	9
5 Transient ischemic attacks only	17	14

Its area includes all the lateral and inferior part of the frontal lobe cortex and white matter the motor cortex (areas 4 and 6 the centers for contraversive eye movements and in the dominant hemisphere the motor speech area of Broca) the lateral and inferior part of the parietal lobe cortex and white matter (sensory cortex angular and supramarginal convolutions) the lateral and superior parts of the temporal lobe and the insula The penetrating branches of the middle cerebral artery supply the putamen outer globus pallidus the posterior limb of the internal capsule above the plane of the upper border of the globus pallidus the adjacent part of the corona radiata the body of the caudate nucleus and the superior portion of the head of the caudate nucleus (Fig 192)

The middle cerebral artery is the most frequently affected artery in embolic and thrombotic cerebrovascular disease It may be occluded in its stem [3] blocking the mouths of the penetrating vessels as well as the flow to the superficial (cortical) vessels or its major branches can be involved individually Foix and Levy recognized eight territorial syndromes (1) total middle cerebral infarction (deep and superficial) (2) major deep middle cerebral

[3] The term *stem* refers to the section of artery lying between the origin of the middle cerebral and the first major branching The stem of the anterior cerebral artery lies between its origin and the junction with the anterior communicating artery The stem of the posterior cerebral stretches from its origin to the posterior communicating artery The stem of the internal carotid artery extends from the region of the clinoid process to the bifurcation into the middle and anterior cerebral arteries

prevent infarction If the occlusion is distal to the circle of Willis i e in the stem of one of the cerebral or cerebellar arteries a series of subarachnoid interarterial anastomoses which join many of the branches of the major cerebral arteries end to end may carry sufficient blood into the compromised territory to prevent or lessen the ischemic damage (Fig 195) There is a capillary anastomotic system between adjacent brain arteries that appears always to be the source of some collateral supply probably inconsequential The collateral inflow is occasionally so great that a major trunk can be entirely occluded without visible damage to the parenchyma In other cases occlusion may lead to softening throughout a vast area which extends to the outermost boundaries of the territory nourished by the affected vessel In between these two extremes there are countless variations in the size shape and completeness of an infarct depending on factors such as the availability of collateral flow the speed of occlusion (time for compensation) and the level of the systemic blood pressure For convenience these factors (the most important of which is the anastomotic circulation) may be called the *ischemia modifying factors* These factors and possibly others such as hypoxia increased cerebral metabolism and altered physical state of the blood may also at times operate adversely to produce ischemia in the territory of partially occluded vessels

The Clinical Picture In general the evolution of the total clinical picture in cerebral thrombosis is much more variable than in embolism and hemorrhage In approximately 80 per cent of cases the main part of the stroke (paralysis or other deficit) is preceded by minor signs or by one or more transient warning ischemic attacks which in a sense herald the oncoming vascular catastrophe *A history of such prodromal episodes is of paramount importance in establishing the diagnosis of cerebral thrombosis* Such episodes do not precede intracerebral hemorrhage and are uncommon with embolism Transient warning attacks may consist of paralysis of a part of the body a unilateral numbness dizziness diplopia impaired vision in one or both eyes dark vision dysarthria headache head pain deafness etc depending on the part of the brain involved They last from a few seconds to an hour or so and the final stroke may be preceded by hundreds of them or by only a single one The stroke may come within a day of the first one or may be delayed for weeks or even months When these minor ischemic attacks are not part of the picture one must depend on other factors in identifying the cerebrovascular process as one of cerebral thrombosis

The main part of the thrombotic stroke whether or not it is preceded by warning attacks develops in one of several ways There may be but a single attack the whole illness developing at once The patient may awaken in the morning with a full blown paralysis or deficit of some other kind or have it come on shortly after arising perhaps while eating breakfast Another pattern is for the stroke once it commences to have a stuttering progression in the next few hours Or a partial stroke may develop and after the patient has improved for several hours a full paralysis may develop Again after one or more fleeting episodes there may be a longer lasting attack succeeded in a day or two by the occurrence of a complete and permanent paralysis The affection may involve several parts of the body simultaneously or as not infrequently happens one part e g a limb or one side of the face is first paralyzed and the other parts become involved serially in steplike fashion until the stroke is fully developed This may take several days or weeks during which time there may be *transient* episodes of improvement or worsening All these various modes of development bespeak cerebral thrombosis It might be added that in transitory attacks and the abrupt episodes of progression which are such common features the temporal profile of the stroke syndrome is duplicated in miniature In thrombotic strokes either the onset or progression of the stroke is particularly common during sleep or shortly after arising (60 per cent of cases) Occasionally a thrombotic stroke comes on in what appears to be a slow gradual fashion but in most of these cases careful inquiry will reveal an uneven or saltatory progression and actually there are only a few patients in whom it can be said that the evolution of the thrombotic stroke was truly gradual over a period of several days Table 131 shows the way in which the clinical picture developed in 125 cases of cerebral thrombosis diagnosed clinically for the most part

Headache is commonly associated with cerebral thrombosis generally being on one side in the front part of the head in occlusion of the carotid system and at the back of the head or in the forehead in basilar disease Many exceptions are to be noted however in which there is no headache at any time either before or during the thrombotic stroke The headache is usually not so violent as in cases of intracranial hemorrhage Its cause is unknown Presumably it is related in some way to the disease process within the vessel since it may antedate the other symptoms of the stroke Stiffness of the neck rarely occurs with cerebral infarction and when it does is related to temporal lobe or cerebellar herniation

The patient although usually elderly is not invariably so and persons in the fourth decade or even younger may be stricken Hypertension an important aggravating factor in atherosclerosis is more often present than not Diabetes is not un

agraphia alexia (visual verbal agnosia)] acalculia (inability to calculate) finger agnosia (inability to recognize fingers and parts of the body) and right left disorientation (inability to tell right from left) The last four of these symptoms comprise the well known *Gerstmann s syndrome* (see Chap 27) Ideational apraxia is another common finding This is an inability to carry out a purposeful act, presumably because of the faulty function of that part of the brain which conceives and initiates a desired performance with the result that the motor apparatus is not guided through the proper series of movements In partial lesions these symptoms may occur singly or in various combinations When the

AREA FOR CONTRAVERSION OF EYES AND HEAD
Rol d A
MOTOR
SENSORY
MOTOR SPEECH AREA (MOTOR APHASIA)
TRUNK
ARM
FINGERS
THUMB
FACE
TONGUE
A I P etal A.
Post Po t l A.
P of d c A.
A g l A
S p-D l s o f Middl Ce b ol A.
Lat ol O b lo f l l A.
I f D s of M ddle C eb l A
VISUAL RADIATIO
VISUAL CORTEX
SENSORY SPEECH AREA (SENSORY APHASIA)
M ddl C eb l St m
P t T mpo l A
L t l G c l te B dy
Tempor l P l A.
A I T mpo l A
AUDITORY AREA

Fig 193 Diagram of the lateral aspect of the cerebral hemisphere showing the branches and distribution of the middle cerebral artery and the principal regions of cerebral localization Below is a list of the clinical manifestations produced by infarction in the superficial territory of the middle cerebral artery and the corresponding regions of cerebral damage In each case the signs and symptoms are separated from the anatomic area by a colon ( )

Paralysis of the contralateral face arm and leg Somatic motor area and the fibers descending from above to enter the corona radiata

Sensory impairment over the contralateral face arm and leg (pinprick touch vibration position two point discrimination stereognosis tactile localization barognosis cutaneographia) Somatic sensory area

Motor aphasia Motor speech area of the dominant hemi phere

Sensory aphasia [word deafness anomia jargon speech sensory agraphia amusia acalculia alexia finger agnosia right left confusion (the last 4 comprise the Gerstmann syndrome)] Sensory speech area of the dominant hemisphere

Ideational apraxia Sensory speech area (parietal portion)

Apractognosia of the minor hemisphere (anosognosia hemiasomatognosia unilateral neglect dressing apraxia spatial agnosia l ss of topographic memory distortion of visual coordinates con structional apraxia etc) Nondominant *supersensory zone* (area corresponding to speech area in opposite hemisphere)



Homonymous hemian pia (often homonymous inferior quadrantanopia) Optic radiation deep to second tem poral c nvolution

Paraly is of conjugate gaze to the oppos te de Frontal contraversive field or fibers projecting therefrom

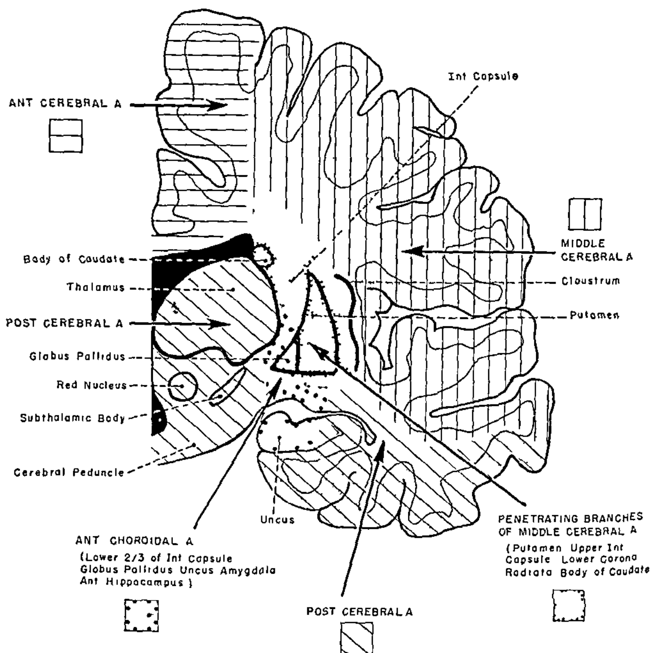


FIG 192 Diagram of a cross section of cerebral hemisphere to show the deep and superficial territories of the major cerebral vessels

infarction (3) partial deep middle cerebral infarction (4) major superficial middle cerebral infarction (5) major posterior middle cerebral infarction (6) partial posterior middle cerebral infarction (7) partial anterior middle cerebral infarction (8) multiple infarction unilateral and bilateral

The classical picture of total superficial and deep middle cerebral infarction is a contralateral hemiplegia hemianesthesia and homonymous hemianopia (Fig 193) If the dominant hemisphere is involved global or total sensorimotor aphasia also is present If the nondominant hemisphere is affected speech is spared but apractognosia of the minor hemisphere is added to the clinical syndrome (see below)

In the middle cerebral territory the motor and sensory cortical zones are spread out over a large area and hence an infarct of restricted size can produce paralysis of the face alone or of only one limb or even part of a limb This restricted deficit is referred to as a *monoplegia* or *monoparesis* (facial brachial crural)

An infarct which lies posteriorly in the superficial middle cerebral territory of the dominant hemisphere may cause hemianopia sensory aphasia [auditory verbal agnosia jargon speech anomia

held responsible for a partial motor speech deficit

Anterior Choroidal Artery A few incomplete clinicopathologic studies have been the basis of present knowledge of the syndrome of the anterior choroidal artery It is said to consist of contralateral hemiplegia hemianesthesia (hypesthesia) and homonymous hemianopia all due to involvement of the posterior limb of the internal capsule and the white matter posterolateral to it through which the first part of the geniculocalcarine fibers pass In the reported cases however the clinical syndrome usually fell far short of what was expected on anatomic grounds Furthermore the practice of surgically occluding the anterior choroidal artery in the treatment of parkinsonism has shown that hemiplegia hemianesthesia and hemianopia rarely occur and in the pathologically studied cases the lesions have been most capricious and indeed in some no lesion at all has been found Because of the present uncertainty surrounding the syndrome no further discussion of it will be given here

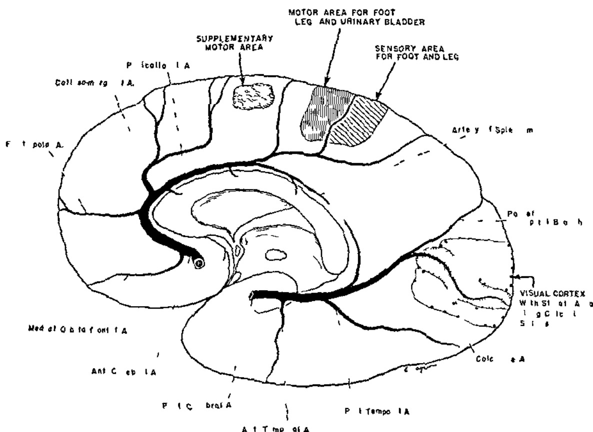


FIG 194 Diagram of the medial aspect of the cerebral hemisphere to show the branches and distribution of the anterior cerebral artery and the principal regions of cerebral localization Below is a list of the clinical manifestations produced by infarction in the territory of the anterior cerebral artery and the corresponding regions of cerebral damage In each case signs and symptoms are separated from the anatomic area by a colon ( )

Paralysis of opposite foot and leg Motor leg area
Lesser degree of paresis of opposite arm Involvement of arm area of cortex or fibers descending to corona radiata therefrom
Cortical sensory loss over toes foot and leg Sensory area for foot and leg
Urinary incontinence Sensorimotor area in paracentral lobule
Motor apraxia of left limb Posterior superior frontal gyri and/or corpus callosum interrupting fibers coming from dominant hemisphere
Grasp reflex sucking reflex and counterholding on the opposite side of the body Medial surface of posterior frontal lobe supplementary motor area(?)
Apraxia of gait (frontal ataxia) Premotor area in superior frontal gyrus
Loss of memory mental impairment Localization not known
Akinetic mutism Bilateral frontal cingulate lesions(?) (Note that aphasia and hemianopia do not occur)

nondominant hemisphere is involved posteriorly apractognosia of the minor hemisphere (a combination of apraxias and agnosias) may dominate the picture or be the only finding This includes anosognosia (unawareness of the illness or disability) left asomatognosia (unawareness of the left side) constructional apraxia (inability to construct a simple object from its parts) loss of topographic memory (inability to revisualize spatial relations e g the floor plan of a house etc) dressing apraxia (inability to dress) etc

If the infarct lies centrally in the motor sensory strip hemiplegia with sensory change will be the chief finding and if situated further anteriorly paralysis often of the monoplegic form with little or no sensory deficit will predominate On the dominant side motor aphasia and agraphia will be present (see Chap 25) On the nondominant side motor impersistence (inability to maintain eyes closed or tongue out or to fix gaze etc) may be noted Deviation of the eyes to the side of the lesion (i e paralysis of conjugate lateral gaze to the opposite side) is extremely common with acute lesions of the anterior part of the middle cerebral territory

When the deep territory of the middle cerebral artery is involved i e the upper part of the posterior limb of the internal capsule the adjacent part of the corona radiata the putamen and the outer part of globus pallidus a total hemiplegia usually results face arm and leg being affected together rather than in monoplegic form This is because the motor fibers lie closely packed in the capsule and therefore destruction is less likely to single out the fibers to only one limb than it is in the cortex where the motor area extends over a wide territory The aphasic disorder if any which results from these deep lesions has not been sufficiently studied

Damage to the basal ganglions (putamen caudate) produces no specific clinical effects which have so far been recognized A hemianopia does not occur as a rule in lesions in the territory of the penetrating arteries since the optic radiation lies at a more inferior level

Hypertension combined with atherosclerosis results in thrombotic occlusion of individual penetrating branches running to the internal capsule and putamen and the resultant small infarctions 2 to 8 mm in extent are called *lacunes* When they involve the internal capsule a mild hemiplegia results recovery from which is often nearly complete Multiple *lacunes* involving the corticospinal and corticobulbar motor tracts cause the clinical picture of pseudobulbar palsy (more appropriately called *bipyramidal palsy*) featuring bilateral upper motor neurone signs i e spasticity increased tendon reflexes Babinski sign dysarthria and dysphagia Spasms of excessive crying or laughing marche a petit pas and mental impairment are also part of the picture *Lacunes* are sometimes said to be the basis of so called arteriosclerotic parkinsonism but it is doubtful if such an entity exists

Anterior Cerebral Artery The anterior cerebral artery through its cortical branches supplies the anterior four fifths of the medial surface of the cerebral hemisphere and also the medial part of the orbital surface of the frontal lobe the frontal pole a strip of the lateral surface along the superomedial border and the anterior seven eighths of the corpus callosum The deep branches which arise near the circle of Willis run chiefly to the anterior limb of the internal capsule and inferior part of the head of the caudate nucleus (see Fig 194)

Well studied cases of infarction of the territory of the anterior cerebral artery are not common and the syndrome of this artery has not been clearly determined as yet Again the clinical picture will depend on the size and location of the infarct which in turn depend on the site of the occlusion the pattern of the circle of Willis and the other ischemia modifying factors Occlusion of the stem of the anterior cerebral artery proximal to the anterior communicating artery is usually well tolerated since collateral flow will cross over from its mate of the opposite side The maximal disturbance occurs when both anterior cerebral arteries happen to arise from one anterior cerebral stem occlusion of the stem then results in a devastating infarction of the anterior cerebral territory of both hemispheres This may include bilateral pyramidal signs with paraplegia and profound mental symptoms The typical syndrome resulting from occlusion of one anterior cerebral artery distal to the circle of Willis includes paralysis and a cortical sensory deficit of the opposite lower limb (paracentral sensorimotor area) and possibly involvement of the opposite arm (fibers descending from the arm area through the central white matter to the internal capsule) mental changes such as forgetfulness akinetic mutism (lack of impulse and animation) motor apraxia (a localized inability to use a limb or a part to carry out a simple coordinated act) of the nondominant upper extremity grasping and sucking reflexes a special type of resistance to passive movement of the limbs (counterholding or *gegenhalten*) and incontinence of bowel and bladder The degree of impairment of sensory and motor function is variable Occlusion of individual branches of the anterior cerebral artery causes only a part of the total syndrome Hemianopia does not occur in anterior cerebral lesions nor has an aphasic difficulty been reported except in rare instances where a softening in the central white matter supplied by the penetrating or deep branches has been

The interpeduncular branches arising near its origin penetrate the brain stem to supply the red nucleus subthalamic nucleus of Luys substantia nigra the most medial part of the cerebral peduncle the oculomotor nucleus the reticular substance of the midbrain decussation of the superior cerebellar peduncles rubrothalamic tract medial longitudinal fasciculus and the medial lemniscus The thalamo perforating branches also arise here and pass to the inferior mesial and anterior parts of the thalamus Branches arising serially along the parent vessel as it encircles the midbrain supply the cerebral peduncle lateral part of the medial lemniscus corpora quadrigemina pineal gland lateral geniculate bodies choroid plexus and hippocampus The thalamogeniculate branches supply the pulvinar

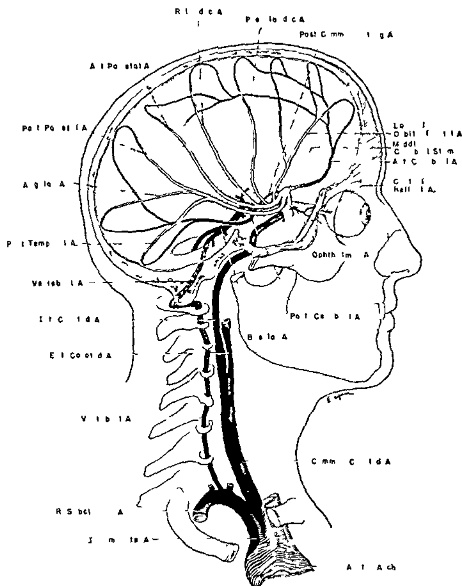


Fig 195 Drawing to illustrate the arrangement of the major arteries carrying blood from the heart to the brain (only the right side is shown) The posterior communicating artery connects the internal carotid and the posterior cerebral arteries forming an important anastomosis between the carotid and basilar systems Further distally the subarachnoid interarterial anastomoses which link the middle cerebral with the anterior and posterior cerebral arteries are shown The ophthalmic and central retinal arteries have been included *to remind* the student that observations and measurements of the retinal circulation provide information concerning the carotid circulation

Internal Carotid Artery The clinical picture of occlusion of the internal carotid artery is very variable Not infrequently occlusion is completely asymptomatic while in other cases it produces a devastating massive infarction which leads to death in a few days Between these two extremes lies every shade of variation As a rule the infarct involves the middle cerebral territory but when the anterior communicating artery is very small the ipsilateral anterior cerebral territory may be affected too in which case the anterior part of the hemisphere (the frontal lobe) bears the brunt of the insult while the region posterior to the rolandic fissure tends to be spared When both anterior cerebral arteries arise from a common stem on one side infarction may involve the anterior cerebral territory bilaterally Likewise the posterior cerebral artery may be supplied from the internal carotid rather than from the basilar artery in which case its territory too may be softened and thus the entire hemisphere and even part of the other may be involved Not infrequently the territory of the anterior choroidal artery is infarcted too When one carotid has been asymptomatically occluded at a previous time occlusion of the other can result in bilateral hemispheric infarction

In symptomatic occlusion of the internal carotid artery the picture usually resembles that of middle cerebral occlusion with a contralateral hemiplegia and hemihypesthesia and aphasia when the dominant hemisphere is involved The relative sparing of the posterior part of the hemisphere is reflected in a low incidence of homonymous hemianopia When the anterior cerebral territory is also involved the clinical picture will include some or all of the features already mentioned under anterior cerebral territory Patients with infarction in the combined territories of the middle and anterior cerebral arteries are much less responsive than those with lesions in only one territory and often they are in a state of light coma No special signs attributable to anterior choroidal involvement have so far been identified

In addition to supplying the brain the internal carotid artery is also the source of blood supply for the optic nerve and retina via the ophthalmic artery (Fig 195) Thus in some instances of carotid occlusion the picture of central retinal artery occlusion is found contralateral to the hemiplegia a puzzling picture until the underlying vascular arrangement is recalled Transient monocular blindness may have occurred intermittently as a warning symptom prior to the onset of the stroke

Whereas most cerebral vessels are inaccessible within the skull and topical diagnosis is made only by inference in carotid occlusion more direct diagnostic tests are available Pulsation may be lacking in the internal common or external carotid arteries when they are palpated in the neck or when the internal carotid artery is palpated in the pharynx Also pressure in the central retinal artery is often reduced on the side of the carotid occlusion and a pressure difference in the two eyes on careful ophthalmodynamometry will point strongly to carotid occlusion Another test consists of compressing the patent opposite carotid artery in the neck precipitating unconsciousness or seizures but such a maneuver cannot be recommended for routine use An additional sign of carotid occlusion is the presence on the opposite side of an intracranial murmur which may be heard by the patient or the examiner or both this murmur is presumably due to enhanced blood flow through the remaining patent vessel The bruit is heard best by placing the bell of the stethoscope over the eyeball but in some cases it is also heard over the temple or cheek When headache associated with cerebral thrombosis or embolism is unilateral and situated just above the eyebrow involvement of the middle cerebral or internal carotid artery is suggested

The common carotid arteries may be occluded at their origin particularly in "pulseless disease or the *aortic arch syndrome* The neurologic symptoms and signs of carotid occlusion just discussed may or may not be present depending on the adequacy of the circle of Willis and of the vertebral basilar system The following manifestations for the most part nonneurologic have been reported in the aortic arch syndrome absence of pulsation in carotid and radial arteries faintness on arising from the horizontal position recurrent loss of consciousness headache neck pain paresthesias of various parts of the body transient blindness (unilateral or bilateral) dimness of vision with exercise premature cataracts retinal atrophy and pigmentation atrophy of the iris leukomas peripapillary arteriovenous anastomoses optic atrophy claudication of the jaw muscles perforation of the nasal septum saddle nose deformity trophic ulceration of the face facial atrophy (unilateral or bilateral) indolent infections of the face abnormal facial pigmentation and loss of hair This condition was originally described in Japan particularly in young Japanese women who were found to be suffering from a granulomatous arteritis (Takayasu s disease see Chap 229) The majority of the authors cases of pulseless disease have been due to severe atherosclerosis

Vertebral basilar posterior cerebral System *Posterior Cerebral Artery* The terminal or cortical branches of this vessel supply the undersurface of the temporal and occipital lobes as well as the entire medial surface of the occipital lobe including the visual area (areas 17 18 and 19) Many important branches arise from the more proximal part of the artery between its origin at the bifurcation of the basilar artery and the cortical distribution

tion) tend to be associated with an inferior quadrantanopia More often the defect is hemianopic When only the central part of the visual field is affected there may be a hemianopic scotoma Scintillating phenomena i e flashes of light crude white or colored figures which suddenly appear in the affected part of the visual field are not uncommon The patient s awareness of the visual disturbance is variable He may be totally unaware of the defect which is discovered for the first time by the examiner or he may have vaguely appreciated that something was wrong with one eye In the acute stages with large temporooccipital lesions the opposite extreme may be encountered in that the patient reports that he is able to see only one half of objects or words or states that he is totally blind when he obviously is not When the lesion lies in the dominant hemisphere a dysphasic disturbance not yet clearly delineated may result The most prominent feature of it is alexia the patient reading very laboriously and having great difficulty in seeing letters but when given sufficient time comprehending what he reads The reading material is sometimes held at an angle and in rare instances the patient may read better when the lines are placed vertically The capacity for re visualization of spacial relationships (the ability to imagine the topography of home or town) may be lost and the ability to name persons may be impaired With large lesions of the dominant hemisphere temporary disorientation and memory loss occur possibly because of damage to the hippocampal and lingual gyri Color blindness total or in the half field is a prominent finding Visual object agnosia (inability to recognize objects) tactile agnosia or asymbolia metamorphopsia (objects appearing too small or too large or distorted) and simultanagnosia (inability to synthesize the elements of a scene into a whole) also occur

Bilateral lesions of the occipital lobes if extensive cause total blindness of the cortical type because of a bilateral homonymous hemianopia The pupillary reflexes are retained and fundoscopically the optic nerves are normal unlike blindness from retinal and optic nerve or tract disease Often the patient is unaware of the blindne s and may in fact deny it when questioned specifically And with bilateral lesions there is usually a loss of memory which varies from case to case More commonly the bilateral lesions are incomplete and the patient is left with a sector of visual field intact In small calcarine lesions there may be loss of central vision only (bilateral homonymous central scotomas) or on the other hand in larger calcarine lesions only central vision may be spared and vision is likened to looking through a narrow pipe

When occlusion of the posterior cerebral artery occurs more proximally (one might speak of anterior syndromes) the clinical picture will comprise signs of damage to thalamus cerebral peduncle midbrain and hypothalamus and in addition the manifestations just described (hemianopia etc) may or may not be present depending on the collateral inflow of blood Best known is the *thalamic syndrome* of Dejerine and Roussy which results from infarction of the region of the sensory nucleus in the posterolateral part of the thalamus (supplied by the thalamogeniculate vessel) The lesion may be so small as to be overlooked on pathologic examination The central feature is a sensory loss on the opposite side of the body usually affecting deep and superficial sensation (pain temperature touch proprioception) or rarely it may be of the dissociated type either pain and temperature or vibratory and position sense being affected while other sensory modalities are relatively spared It may take a monoplegic pattern Often there is an associated intractable agonizing pain in the affected parts of the body (thalamic pain) occurring spontaneously and augmented by all types of stimulation of the affected parts Hyperpathia and taste disorders are common In other patients spontaneous pain may be entirely missing In the motor sphere there may be a mild evanescent hemiparesis and in some patients the affected limbs show hemiballismus choreoathetosis incoordination intention tremor asynergy cramplike spasms and a postural abnormality of the hand (cf Chap 26) The mind is usually strikingly spared

Occlusion of the stem of the posterior cerebral artery may lead to a hemiplegia owing to infarction of the cerebral peduncle but this appears to be rather rare Occlusion of the thalamoperforate branches which originate from the most medial part of the posterior cerebral stem gives rise to several different syndromes depending on the branches involved (1) a superior syndrome in which the upper part of the red nucleus or rubrothalamic tract is involved producing on the opposite side of the body a gross ataxia (see Chap 26) (2) an inferior syndrome (Claude s syndrome) in which homolateral cerebellar signs and a third nerve palsy are combined (3) Weber s syndrome i e a third nerve palsy combined with a contralateral hemiplegia (see Chap 30) (4) *hemiballismus* which probably arises also from an occlusion of the branch of the posterior cerebral artery running to the subthalamic nucleus of Luys (5) paralysis of conjugate vertical gaze and at times of lateral gaze which results from damage to the tegmentum and tectum of the midbrain area (6) peduncular hallucinosis (visual hallucinations of brightly colored scenes and objects) have been observed in occlusion of the posterior cerebral artery but the site of the lesion has not been determined More often an intra

and the lateral nuclei of the thalamus (Fig 196)

Again the clinical picture resulting from occlusion will depend on the site of the obstruction the site and size of the infarct and the ischemia modifying factors Occlusion proximal to the posterior communicating artery may be tolerated if collateral flow via that vessel is adequate however the penetrating branches arising from the stem of the posterior cerebral artery may be occluded at their mouths Even distal to the posterior communicating artery occlusion may cause no damage if collateral flow via the subarachnoid interarterial anastomoses is sufficient

Classically occlusion of the cortical or superficial branches of the posterior cerebral artery gives rise to a contralateral homonymous hemianopia because of involvement of the primary visual area in the calcarine region Partial visual field defects are common and it is claimed that posterior cerebral lesions are likely to cause a superior homonymous quadrantanopia whereas middle cerebral lesions (involving the superior portion of the optic radia

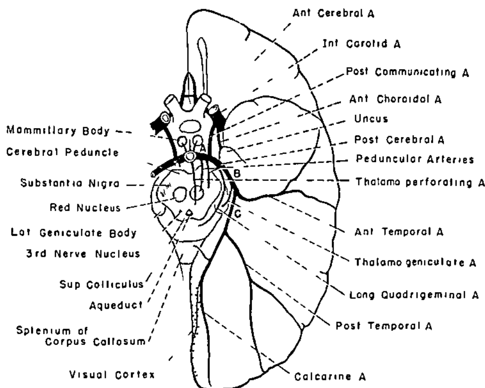


FIG 196 Diagram of the inferior aspect of the brain to show the branches and distribution of the posterior cerebral artery and the principal anatomic structures Below is a list of the clinical manifestations produced by infarction in the territory of the posterior cerebral artery and the corresponding regions of damage In each case the signs and symptoms are separated from the anatomic area by a colon ( )

Homonymous hemianopia (often upper quadrantic) Calcarine cortex or optic radiation nearby Hemiachromatopsia may be present

Bilateral homonymous hemianopia cortical blindness agnosia for blindness Bilateral calcarine cortex

Dyslexia visual agnosia associated tactile agnosia perseveration Calcarine and pericalcarine cortex in *dominant* hemisphere

Memory defect Hippocampal lesion bilaterally or on dominant side(?)

Thalamic syndrome—sensory loss (all modalities) spontaneous pain choreoathetosis intention tremor spasms of hand mild hemiparesis Posteroventral nucleus of thalamus in territory of thalamogeniculate artery (involvement of the latter results in hemiballismus) and also the subthalamic body

Thalamoperforate syndrome—cerebellar ataxia and third nerve palsy Third nerve and the red nucleus or rubrothalamic tract

Weber s syndrome—third nerve palsy and contralateral hemiplegia Third nerve and cerebral peduncle

Contralateral hemiplegia Cerebral peduncle

Paralysis of vertical eye movement Supranuclear fibers to third nerve(?)

Coma Damage to upper brain stem (midbrain thalamus)

Decerebrate attacks Damage to upper brain stem (especially motor tracts)

Static tremor has been omitted because of the uncertainty of its occurrence in the posterior cerebral syndrome

branch to the pyramid is occluded that part of the corticospinal tract may be infarcted unless collateral flow is adequate Of course each of these branches may become occluded somewhere along its course after leaving the vertebral artery and produce similar effects Rarely occlusion of the vertebral artery or one of its medial branches produces infarction of the pyramid in combination with involvement of the medial lemniscus and the emergent hypoglossal fibers [contralateral paralysis of *arm and leg (face spared) contralateral loss of* touch and vibration sense and ipsilateral wasting of the tongue] This is the medial medullary syndrome (see Fig 197D) Finally vertebral occlusion can lead to symptoms by blocking the posterior inferior cerebellar artery

The posterior inferior cerebellar artery supplies *the inferior portion of the lateral medullary region* the restiform body and the underbelly of the cerebellar hemisphere Occlusion may occur at its mouth in association with vertebral occlusion or anywhere along its course Some patients tolerate obstruction of this vessel with little or no ill effect in others an extensive cerebellar infarct results It should be pointed out that the various cerebellar arteries are connected to their neighbors by subarachnoid interarterial anastomoses in the same way as the main cerebral arteries and the potential *for collateral flow to a compromised territory is* excellent

The clinical picture resulting from occlusion of the posterior inferior cerebellar artery is highly variable Often no serious damage results At other times there may be dizziness homolateral cerebellar ataxia nystagmus and loss of equilibrium *due to involvement of the inferior surface of the*

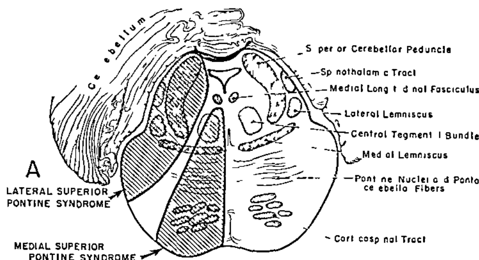


FIG 197A

1 MEDIAL SUPERIOR PONTINE SYNDROME (paramedian branches of upper basilar artery)

Signs and symptoms	*Structures involved*
On side of lesion	
Cerebellar ataxia (probably)	Pontine nuclei pontocerebellar fibers
Internuclear ophthalmoplegia	Medial longitudinal fasciculus
Myoclonic syndrome palate pharynx vocal cords respiratory apparatus face oculomotor apparatus	Central tegmental bundle? (localization *not agreed* upon)
On side opposite lesion	
Paralysis of face arm and leg	Corticobulbar and corticospinal tract

2 LATERAL SUPERIOR PONTINE SYNDROME (syndrome of superior cerebellar artery)

On side of lesion	
Ataxia of limbs and gait falling to side of lesion *nystagmus*	Middle and superior cerebellar peduncles superior sur*face of cerebellum* dentate nucleus
Miosis ptosis decreased sweating over face (Horner s syndrome)	Descending sympathetic fibers
Static tremor reported in one case	Dentate nucleus(?) superior cerebellar peduncle(?)
On side opposite lesion	
Impaired pain and thermal sense over limbs and half of body	Spinothalamic tract

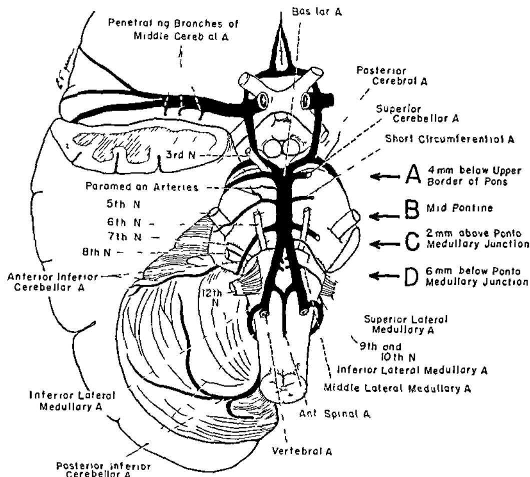


FIG 197 Diagram of the brain stem showing the principal vessels of the vertebral basilar system The letters and arrows on the right indicate the levels of the four cross sections A B C and D which follow Although typical vascular syndromes of the pons and medulla have been designated by sharply outlined shaded areas the student must appreciate that since satisfactory clinicopathologic studies are far from numerous the diagrams are not necessarily accurate nor do they always represent established fact The great frequency with which infarcts fail to produce a well recognized syndrome and the special tendency for syndromes to merge with one another must be emphasized

cerebral hemorrhage is responsible All these abnormalities are relatively uncommon in cerebrovascular disease Finally (7) extensive infarction of the upper midbrain results in deep coma and decerebrate rigidity (reflex extensor posture)

Vertebral Artery The vertebral arteries are the chief arteries of the medulla and each supplies the lower three fourths of the pyramid the medial lemniscus the lower half or more of the retroolivary region (the lateral medullary region) the restiform body and the posteroinferior part of the cerebellar hemisphere (see Fig 197) The relative size of the vertebral arteries varies a good deal and in approximately 10 per cent of cases one vessel is so small that the other can be considered the only artery of supply to the brain stem In this case depending on collateral inflow from the carotid system via the circle of Willis occlusion would be equivalent to occlusion of the total vertebral basilar system including the posterior cerebral arteries The posterior inferior cerebellar artery is usually a branch of the vertebral artery but not infrequently it has a common origin with the anterior inferior cerebellar artery from the basilar artery It is necessary to keep these anatomic variations in mind when visualizing the effects of vertebral artery occlusion

It would appear that when there are two good sized vertebral arteries occlusion on one side occurs not infrequently without any recognizable symptoms and signs or pathologic changes If the occlusion of the vertebral artery is so situated as to block the mouth of the middle artery of the lateral medulla the lateral medullary syndrome may be precipitated (see below) When the branch to the anterior spinal artery is blocked collateral influx from the spinal artery branch of the opposite side is usually sufficient to prevent infarction If the

separately e g superior cerebellar anterior inferior cerebellar superior lateral medullary artery etc It is convenient to separate the branches of the basilar artery into (1) paramedian seven to ten in number supplying a wedge of pons on either side of the midline (2) the short circumferential branches five to seven in number supplying the lateral two-thirds of the pons and the middle and superior cerebellar peduncles and (3) the long circumferential two in number to the cerebellar hemispheres (superior and anterior inferior cerebellar arteries) In occlusion of the basilar artery one might expect a vast array of clinical manifestations since the artery supplies a large number of structures (pontine nuclei corticospinal and corticobulbar tracts the cerebellum and middle and superior cerebellar peduncles medial and lateral lemnisci spinothalamic tracts medial longitudinal fasciculi

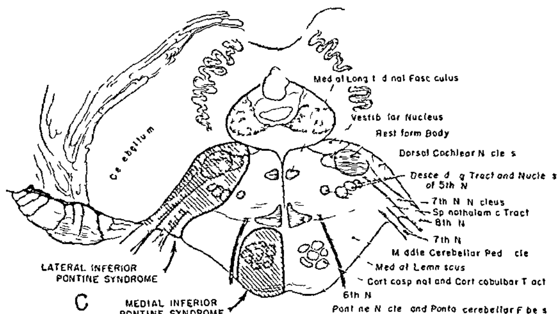


Fig 197C

5 MEDIAL INFERIOR PONTINE SYNDROME (occlusion of paramedian branch of basilar artery)

Signs and symptoms	*Structures involved*
On side of lesion	
Paralysis of conjugate gaze to side of lesion (preservation of convergence) nystagmus	Center for conjugate lateral gaze
Ataxia of limbs and gait	Pontine nuclei(?) pontocerebellar fibers(?)
Diplopia on lateral gaze	Abducens nerve
On side opposite lesion	
Paralysis of face arm leg	Corticobulbar and corticospinal tract in lower pons
Impaired tactile and proprioceptive sense over half of the body (of uncertain occurrence)	Medial lemniscus

6 LATERAL INFERIOR PONTINE SYNDROME (occlusion of anterior inferior cerebellar artery)

On side of lesion	
Deafness(?) tinnitus	Auditory nerve
Nystagmus vertigo nausea vomiting	Vestibular nerve or nucleus
Facial paralysis	Seventh nerve
Paralysis of conjugate gaze to side of lesion diplopia	Center for conjugate lateral gaze
Ataxia	Middle cerebellar peduncle
Impaired sensation over face (uncommon)	Descending tract and nucleus fifth nerve
On side opposite lesion	
Impaired pain and thermal sense over half of the body (may include the face)	Spinothalamic tract

7 TOTAL UNILATERAL INFERIOR PONTINE SYNDROME (occlusion of anterior inferior cerebellar artery) Combination of lateral and medial syndromes

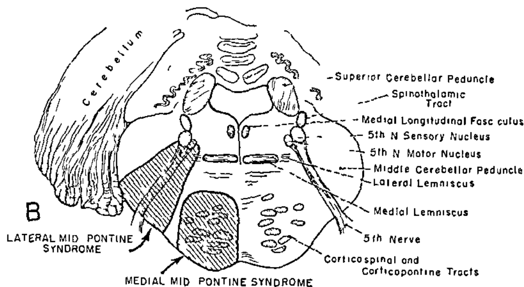


Fig 197B

3 MEDIAL MIDPONTINE SYNDROME (paramedian branch of midbasilar artery)

Signs and symptoms	*Structures involved*
On side of lesion	
Ataxia of limbs and gait (more prominent in bilateral involvement)	Pontine nuclei and pontocerebellar fibers
On side opposite lesion	
Paralysis of face arm and leg	Corticobulbar and corticospinal tract
Variable and transient impaired touch and proprioception (this has not been clearly established)	Medial lemniscus

4 LATERAL MIDPONTINE SYNDROME (short circumferential artery)

On side of lesion	
Ataxia of limbs	Middle cerebellar peduncle
Paralysis of muscles of mastication	Motor fibers or nucleus fifth nerve
Impaired sensation over side of face	Sensory fibers or nucleus fifth nerve

cerebellum and its connections with the brain stem Then again the *lateral medullary syndrome* may be evoked through blockage of flow along the inferior artery of the lateral medulla While occlusion of the posterior inferior cerebellar artery is usually stated to be the cause of the lateral medullary syndrome this appears to be true in only a minority of patients more careful studies have shown that in many instances occlusion of another vessel originating at a higher level a branch of either the vertebral or the lower basilar artery is responsible

The lateral medullary syndrome is produced by infarction of a small wedge of lateral medulla lying posterior to the inferior olivary nucleus (see Fig 197D) The classical syndrome consists of pain and numbness of the ipsilateral face (descending tract and nucleus of the trigeminal nerve) dizziness nausea vomiting nystagmus (vestibular nucleus or fibers) dysphagia ipsilateral palatal weakness hoarseness ipsilateral paralysis of vocal cord (nucleus ambiguus or issuing fibers) homolateral cerebellar ataxia of arm and leg disequilibrium with falling to the side of the lesion (cerebellum inferior cerebellar peduncle or olivocerebellar fibers) sensory loss (dissociated loss of pain and temperature sensation) on the opposite side of the body below the neck—sometimes the face is included (spinothalamic tract) ipsilateral Horner s syndrome (descending sympathetic tract) and hiccoughs Added to the basic picture there may be ipsilateral loss of taste (tractus solitarius) diplopia skew deviation or internuclear ophthalmoplegia (the medial longitudinal fasciculus vestibular connections or perhaps the sixth nerve) contralateral corticospinal signs (pyramid) loss of the knee jerks ipsilateral peripheral facial palsy paresthesias of the ipsilateral side hippus and trophic ulceration Many of these additional signs indicate extension of the lesion to a slightly higher level This syndrome one of the most striking in neurology is almost always due to vascular disease

Basilar Artery The basilar artery supplies not only the pons and upper cerebellum but in most cases both posterior cerebral territories too The trunk of the basilar artery itself may be occluded or any one of its many branches may be involved

vestibular and cochlear nuclei descending hypothalamospinal sympathetic fibers the upper medulla and cranial nerves III IV V VI VII VIII (the nuclei the segment within the brain stem and the peripheral nerve itself) see Fig 197]

Basilar occlusion may arise in several ways thrombosis may occur on an atherosclerotic plaque in the lowermost basilar artery near its origin both vertebral arteries may become occluded by atherosclerotic thrombosis closure of the second being equivalent to basilar obstruction atherosclerotic occlusion of a single vertebral (when there is only one of good size) is equivalent to basilar occlusion atherosclerotic thrombosis may involve only a branch rather than the trunk of the basilar artery *and this is probably the commonest cause of basilar* symptomatology finally *the obstruction* may be embolic the embolus usually lodging at the upper bifurcation of the basilar or in one or other posterior cerebral artery since *if it is small enough* to pass through the vertebral artery it should easily traverse the length of the basilar artery which is usually of greater diameter than either vertebral artery

In the complete basilar syndrome *examination* shows principally paralysis of all *four extremities* (usually *one side is more affected than the other*) and the bulbar musculature dysarthria dysphagia diplopia and sensory loss for pain *temperature* touch and vibration (motor paralysis *usually* predominates over sensory deficit) and perhaps impaired vision At the most advanced stage of the illness the patient is deeply comatose both voluntary and reflex eye movements are *absent* the pupils are fixed to light and may be dilated *respirations* are irregular the systemic blood pressure fluctuates and accesses of extensor rigidity may be evoked by pinch or other stimuli *Occasionally* with low pontine lesions the patient although totally paralyzed may be relatively alert but physically powerless to evince signs of the retained alertness except through signaling with eye *blinks* or eye movements (see p 311)

When the full basilar artery syndrome has developed it is usually not difficult to make the correct diagnosis The aim should be however to recognize basilar insufficiency before the stage of total deficit has been reached The early manifestations occur in many combinations and it would be difficult to list all the possibilities Most commonly the following will be encountered weakness or paralysis of one or both sides of the body occasionally a monoplegia only numbness and a corresponding sensory loss involving one entire side of the body or both sides of the body or one or both sides of the face or both hands or both legs or numbness of one side can be combined with paralysis of the other dysarthria speechlessness stuttering and dysphagia dizziness of a vestibular type either in attacks or upon change of posture often associated with nausea and vomiting diplopia due to a disturbance of the third or sixth nerves or resulting from faulty conjugate lateral gaze or internuclear ophthalmoplegia (see p 281) paralysis of conjugate lateral gaze to the side of the *lesion* (this is the reverse of hemispheric lesions where the patient is unable to turn his eyes toward the side of the paralysis) cerebellar ataxia involving the limbs of one or both sides *or affecting chiefly* the functions of walking and standing infranuclear palsy of the seventh nerve (facial paralysis) or the motor part of the fifth nerve (weakness of masseter muscle and deviation of the jaw to the side of the lesion) impaired vision blurred vision dark vision or scintillating scotomas loss of hearing either unilateral or bilateral and rarely tinnitus headache head pain or *peculiar head sensations (like a cord* being drawn tightly around the head) confusion impaired memory drowsiness (the patient may however be lucid) Rarer phenomena include bulbar myoclonus bilateral internuclear ophthalmoplegia facial fasciculations or twitchings simple auditory hallucinations and distortions of taste

It has already been pointed out that occlusion of individual basilar branches is very frequent In the case of the *superior cerebellar artery* the main signs are severe ipsilateral cerebellar ataxia (middle and/or superior cerebellar peduncles) instability of gait (involvement of the medial part of the superior surface of the cerebellum) nausea and vomiting slurred speech and loss of pain and temperature over the extremities body and face of the opposite side (spinothalamic tract) Partial deafness a static tremor of the ipsilateral upper extremity Horner s syndrome and bulbar myoclonus have also been reported In *occlusion of the anterior inferior cerebellar artery* it is well to remember that the extent of the infarct is variable The size of this artery and the territory it supplies vary inversely with that of the posterior inferior cerebellar artery The principal findings are ipsilateral cerebellar ataxia (middle cerebellar peduncle) Horner s syndrome ipsilateral deafness whirling dizziness facial palsy and sensory loss over the face Nausea vomiting tinnitus and nystagmus may be associated Pain and temperature sensation may be lost on the opposite side of the body If the occlusion is close to the origin of the artery the corticospinal fibers may also be involved producing a hemiplegia Other branches of the basilar artery may also be occluded individually occlusion of the artery to the retroolivary space will produce the lateral medullary syndrome occlusion of a paramedian branch will result in infarction of the corticospinal fibers on one side and of the adjacent pontine nuclei and pontocerebellar fibers

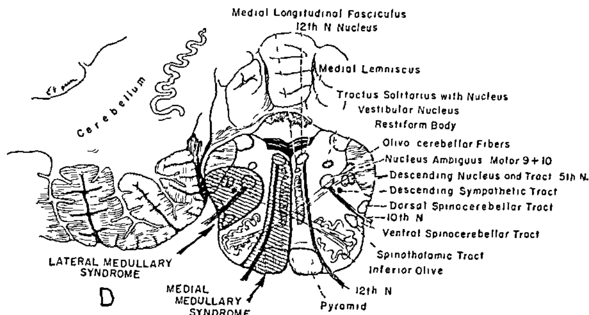


Fig 197D

8 MEDIAL MEDULLARY SYNDROME (occlusion of branch of vertebral or lower basilar artery)

Signs and symptoms	*Structures involved*
On side of lesion	
Paralysis with atrophy of half the tongue	Issuing twelfth nerve
On side opposite lesion	
Paralysis of arm and leg sparing face	Pyramidal tract
Impaired tactile and proprioceptive sense over half the body	Medial lemniscus

9 LATERAL MEDULLARY SYNDROME (occlusion of any of five vessels may be responsible)

On side of lesion	
Pain numbness impaired sensation over half the face	Descending tract and nucleus fifth nerve
Ataxia of limbs falling to side of lesion vertigo nausea vomiting nystagmus	Restiform body spinocerebellar tract vestibular fibers or nucleus
Miosis ptosis decreased sweating (Horner s syndrome)	Descending sympathetic tract
Dysphagia hoarseness paralysis of palate paralysis of vocal cord diminished gag reflex	Issuing fibers ninth and tenth nerves
Loss of taste	Nucleus and tractus solitarius
Hiccoughs also occur	
On side opposite lesion	
Impaired pain and thermal sense over half the body sometimes face	Spinothalamic tract

10 TOTAL UNILATERAL MEDULLARY SYNDROME (occlusion of vertebral artery) Combination of medial and lateral medullary syndromes

11 LATERAL PONTOMEDULLARY SYNDROME (occlusion of anterior inferior cerebellar artery or superior lateral medullary artery) Combination of lateral medullary and lateral inferior pontine syndromes

12 BASILAR ARTERY SYNDROME (the syndrome of the lone vertebral artery is equivalent)
[A combination of the various unilateral brain stem syndromes plus those arising in the posterior cerebral artery distribution Most often the clinical picture consists of bilateral long tract signs (sensory and motor) with cranial nerve and cerebellar disturbances]

Signs and symptoms	*Structures involved*
Paralysis or weakness of all extremities plus all bulbar musculature	Corticobulbar and corticospinal tracts bilaterally
Diplopia paralysis of conjugate gaze nystagmus	Ocular motor nerves apparatus for conjugate gaze medial longitudinal fasciculus vestibular apparatus
Blindness impaired vision various visual field defects	Visual cortex
Bilateral cerebellar ataxia	Cerebellar peduncles and the cerebellar hemispheres
Coma	Tegmentum of midbrain thalami

and the pulse although often not altered to an important extent in cerebral thrombosis may in basilar artery occlusion undergo a terminal rise the temperature rising to 104 to 106 F The blood pressure fluctuates but seldom falls to low levels

One cannot generalize about mental change stupor and coma in cerebral thrombosis for they are in large part related to both the site of the lesion and its massiveness (with secondary pressure effects on diencephalic and midbrain structures) Drowsiness apathy impairment of memory and mild degrees of confusion are extremely common in brain infarction due to cerebral thrombosis especially when the lesion is situated in a cerebral hemisphere However a patient with a complete hemiplegia right or left due to a hemispheral lesion may remain relatively alert and may be found propped up in bed reading or pretending to read the morning newspaper with small lesions of the motor system there may be no discernible intellectual change whatsoever When both the middle and anterior cerebral territories on one side are involved the patient s responses are usually minimal although he is generally awake or can be aroused Massive bilateral lesions of the cerebral hemispheres precipitate deep coma In bilateral lesions of the *basis pontis* almost total paralysis of the entire body musculature may be combined with a surprising degree of awareness but again when the tegmentum of the upper brain stem is softened deep coma results Spasmodic crying or laughing may be seen in unilateral lesions and is not always to be taken as a sign of bipyramidal palsy

When a massive hemispheral infarct has occurred there is always the possibility that severe cerebral swelling will follow in the next few days When this happens tentorial subfalcial or cerebellar herniation may occur and if the midbrain is seriously compressed deep coma dilated fixed pupils respiratory embarrassment and rising temperature presage a hopeless outcome In milder cases the patient passes through an extremely drowsy period and transient papilledema with a raised spinal fluid pressure may be encountered *Decerebrate posture* (reflex extensor rigidity) usually reflects irreversible damage to the midbrain or pons either by softening or as the result of Duret hemorrhages secondary to tentorial herniation and midbrain compression *Unilateral decerebrate posture* is seen not infrequently and does not carry with it the poor prognosis of the bilateral variety

Laboratory Findings Cerebral infarction does not alter renal function and any urinary abnormalities are to be attributed to concomitant renal disease Furthermore it does not occasion an important leukocytosis The cerebrospinal fluid pressure is usually normal in patients with cerebral thrombosis except with large infarcts associated with severe swelling of the damaged tissue Cerebral thrombosis virtually never causes blood in the spinal fluid the latter is usually "crystal clear" unless the infarct is especially congested when a very faint xanthochromia (1 to 2 on a scale of 10) may occur A slight increase in the leukocytes of the spinal fluid (3 to 8 polymorphonuclears) is common in the first few days of the illness Rarely and for unexplained reasons a brisk transient pleocytosis (400 to 2 000 polymorphonuclears per cubic millimeter) occurs on about the third day A persistent increase in the white blood cells of the cerebrospinal fluid suggests the presence of chronic meningitis (syphilis tuberculosis torula) granulomatous arteritis septic embolism cerebral thrombophlebitis or a nonvascular process The total protein may be normal but frequently it is raised to 50 to 80 mg per cent Rarely is it over 100 and when it is some other diagnosis should be seriously considered A Wassermann or some other specific test for syphilis is still routinely made in many clinics but can be dispensed with unless the rest of the clinical and laboratory picture points toward neurosyphilis A positive test in a bloody fluid is not valid since syphilitic reagin may have been carried into the fluid by the contaminating blood Skull x rays are not remarkable and the pineal gland will not be shifted unless severe cerebral swelling has occurred in which case the patient will usually be comatose or stuporous The electroencephalogram is still of limited value in indicating infarction or distinguishing it from hemorrhage and from nonvascular conditions In brain stem and capsular infarction the tracing is usually within normal limits Generally speaking in cerebral infarction the electrical activity is found to be of a slightly slower frequency and lower voltage than normal High voltage slow waves (3 to 5 per second) are evidence in favor of hemorrhage or tumor More thorough clinicopathologic electroencephalographic correlation studies are needed In distinguishing a vascular lesion from brain tumor serial electroencephalograms may be useful in that in the former the tracing tends to improve in the latter to worsen The pneumoencephalogram may be normal in the acute stages of arterial occlusion but later local ventricular dilatation may occur it indicates the site of tissue loss due to infarction This procedure is not recommended as a diagnostic laboratory test in patients with occlusive cerebrovascular disease because of the danger of precipitating a worsening in the neurologic syndrome possibly owing to the hypotensive state which so often attends the introduction of air Carotid arteriography a procedure widely used in many clinics to visualize the site of the vascular occlusion will demonstrate the blocked artery if it is in the carotid or in the proximal parts of the middle cerebral or

on the same side of the pons Smaller infarcts (lacunes) will result from occlusion of the smaller branches in patients with hypertension and athero sclerosis They may be responsible for or contribute to the syndrome of pseudobulbar palsy

One of the hallmarks of a brain stem lesion is the occurrence of bilateral pyramidal tract signs and/or bilateral sensory manifestations within the brain stem tracts descending to or ascending from each side of the body either cross mutually or run very close to one another as opposed to the cere bral hemispheres where the motor and sensory tracts subserving one side of the body are at a distance from those of the other side While it is correct to emphasize that bilaterality of a lesion strongly suggests brain stem involvement it must be pointed out with equal force that unilaterality of a lesion by no means precludes a brain stem site On the contrary in many instances of infarction within the basilar territory the lesion is strictly limited to one side bespeaking occlusion of a basilar branch rather than of the main trunk An other cardinal sign of involvement of the brain stem is evidence of a nuclear or infranuclear lesion of one or more cranial nerves especially if com bined with signs of long tract involvement

Additional manifestations which point unequivo cally to a brain stem lesion are whirling dizziness diplopia cerebellar ataxia Horner s syndrome and deafness Sensory disturbances may also be helpful in localization A dissociated sensory deficit over the face or one half the body (loss of pain and temperature sense and retention of vibration and position sense or vice versa) usually indicates a lesion within the brain stem a sensory loss over one side of the body involving all modalities indi cates a lesion at approximately the thalamic level or higher when position sense two point discrimi nation and tactile localization are affected relatively more than pain temperature and tactile sense a cortical lesion is suggested In the diagnosis of disease of the brain stem it is impossible from motor signs alone to distinguish a hemiplegia of pontine origin from one of cerebral origin except by the aid of coexisting phenomena As with cerebral lesions a flaccid paralysis gives way to spasticity in the following days weeks or months and there is no satisfactory explanation for the variability in this period of delay When both motor and the sensory manifestations are bilateral it is almost unequivocal evidence that the lesion lies infraten torially The several brain stem syndromes illustrate an important point—the cerebellar system spino thalamic tract trigeminal nucleus and the sympa thetic fibers can be involved at different levels Associated phenomena are necessary for the identi fication of the exact level of the lesion

A myriad of eponymic brain stem syndromes e g Weber Claude Benedikt Foville Raymond Cestan Millard Gubler etc already mentioned in pp 290 to 291 have been described with brain stem lesions However most of them relate to cases of tumor and other nonvascular diseases and only occasionally is one of these syndromes en countered in association with vascular disease The diagnosis of vascular disease in this region of the brain is not greatly facilitated by a knowledge of these classical syndromes and it is easier and pref erable to commit to memory the neuroanatomy of the brain stem

The great desirability of being able to categorize the majority of brain stem vascular cases hardly needs to be mentioned However an analysis of the authors personal experience with a large number of these cases shows that too often it has been impossible to either designate the vessel involved or fit the clinical picture to an eponym A survey of the literature indicates that complete neuro pathologic studies in this territory are so few that reliable rules for the exact identification of vessel or vessels involved are not available except for a few of the major syndromes described above There fore it seemed more practical to classify the cases according to the topography of the lesions within the brain stem and to this end the classification seen in Fig 197 was drawn up There are some twelve syndromes in all the principal eight being medial and lateral lesions at four different levels of the brain stem upper pons midpons lower pons and midmedulla Three are simple combinations of a few of the eight syndromes just mentioned while the final syndrome represents a full brain stem infarction This list of syndromes has been useful to the authors in cataloguing many of the day to day clinical cases but it must be appreciated that there are still many patients who do not fit the classification

Further Remarks Concerning Symptomatology In addition to the neurologic manifestations which can be assigned to one or another region of the brain many phenomena whose origin is still ob scure are to be encountered in stroke cases of all types The following remarks relate chiefly to in farction but for the most part they apply also to hemorrhage Cheyne Stokes respiration or a variant thereof is an extremely common finding especially with supratentorial lesions unilateral or bilateral Incontinence of bladder and/or bowel is a regular accompaniment of strokes of moderate to severe degree Vomiting a few times at the onset of a stroke is frequent Sucking and grasping reflexes are extremely common on the side opposite the hemiplegia i e the supposedly unaffected side the grasp reflex showing itself in several ways e g the patient s tendency to palpate rubber tubing or the folds of the bedclothes The temperature

Conversely, the early development of spasticity in the hand grasp reflex and other postural reactions may presage a favorable outcome Bowel and bladder continence usually returns as mental clarity is regained and sphincteric disorders persist only in patients with the most severe hemiplegia or bilateral motor lesions Not uncommonly the hemiplegic limbs are at first tender and ache on manipulation, hindering the physical therapy program Nevertheless physiotherapy should be initiated early in order to prevent fixation contracture at shoulder elbow wrist knuckles knee and ankle a frequent complication and often the source of pain and added disability An annoying unsteady dizzy feeling in the head often persists after damage to the vestibular system in brain stem infarcts

Recurrent cerebral (epileptic) seizures are a complication in some 20 per cent of cases of infarction in which the cerebral cortex has been involved They are infrequent during the period of onset of the thrombotic stroke and usually appear within a few weeks or months It is important not to construe the occurrence of a seizure as an indication of extension of the infarct

Many patients complain of fatigability and are depressed The explanation of these symptoms is uncertain psychologic factors may be important Only a few patients become serious *behavior problems* or psychotic after a stroke but paranoid trends ill temper stubbornness and peevishness are common

Finally in regard to prognosis it must be mentioned that having had one thrombotic stroke the patient is always in danger of another This is especially true in the presence of hypertension

Treatment of Cerebral Thrombosis The treatment of cerebrovascular disease and strokes may be divided into four parts (1) general medical management in the acute phase (2) measures to arrest the pathologic process and restore the integrity of damaged brain tissue (3) physical therapy and rehabilitation (4) preventive measures against strokes and vascular disease

General Medical Management in the Acute Phase In essence this is the care of the comatose or helpless patient (see Chap 272) *Maintenance of the airway* is of great importance The only real danger is pooling of secretions in the pharynx to avoid this the patient must be nursed on his side or in the semiprone position *Pharyngeal suction* is often necessary the larynx or trachea is touched by the tip of the suction tube to stimulate coughing A mouth airway as employed in administering anesthesia can be used if the patient is sufficiently stuporous to tolerate it In a more alert patient when the jaw is held tightly clenched and a nasal feeding tube is in position blocking one side of the nose respiratory exchange may be insufficient and a *tracheostomy* will have to be performed Especially is this necessary when coughing is impossible Oxygen therapy preferably by nasal tube is advisable if aeration of the lungs is compromised in any way *Prevention of pulmonary complications* is best achieved by turning the patient every hour, by strict avoidance of oral feeding if the slightest dysphagia exists and by the use of prophylactic penicillin therapy Constant urinary bladder drainage with daily irrigation regular changing of catheters and urinary antiseptics (Cantrisin in doses of 1 0 Gm per day) is necessary if coma is protracted Intravenous fluids for the first 2 to 3 days followed by transnasal stomach tube feedings are the best means of providing adequate fluid intake and nourishment Other measures include elastic stockings on the legs and correction of cardiac failure and its effects i e edema

Measures to Arrest the Pathologic Process and Restore the Integrity of Damaged Brain Tissue Most of the methods recommended in the handling of acute strokes due to infarction aim to dilate the cerebral arteries and enhance collateral blood flow to the region of brain softening Severely damaged brain tissue cannot be saved but it is suspected that the marginal zones of the infarct and even islands of tissue within the infarct have not been irreversibly injured but are merely receiving insufficient blood and oxygen to maintain normal function Improvement in the blood supply should therefore result in the restoration of function It is speculated also that widespread vasoconstriction or vasospasm occurs in association with sudden vascular occlusion and the use of vasodilators would counteract this aggravating factor (but see the following paragraph)

The following are the more important methods which have been or are being used (1) *Cervical sympathetic block* This procedure has fallen into disuse since careful clinical studies failed to confirm the initial reports of its beneficial effect (2) *Cerebral vasodilators* Despite experimental evidence that these agents increase the cerebral blood flow as measured by the nitrous oxide method they have not proved beneficial in careful studies in human stroke cases This is true of inhalation of 5 per cent carbon dioxide nicotinic acid Priscoline alcohol and papaverine A few clinical trials have indicated that histamine aminophylline and intra arterial papaverine have some merit but further investigation is needed In opposition to the use of these methods is the suggestion that vasodilators are harmful rather than beneficial since by lowering the systemic blood pressure the intracranial anastomotic flow may be reduced (3) *Measures to increase the blood supply to the brain* Clinical observations indicate that strokes and ischemic attacks in many cases develop when the patient gets

anterior cerebral stems However the procedure as practiced at present is not without risk and in patients with vessels narrowed by atherosclerosis the infarction may be extended It is not to be recommended as a routine measure in cerebral thrombosis but for the time being should be used only if the diagnosis of vascular disease is uncertain if vascular surgery is contemplated or as part of a scientific investigation of cerebrovascular disease Radioactive concentration studies (arsenic scan) used for the detection of tumor abscess etc often show a mildly positive picture over infarcts

Course and Prognosis In the introduction it was pointed out that the characteristic temporal profile of a vascular lesion was one of improvement if the patient survives When the patient is seen early in the course of his illness it is extremely difficult to generalize about the *immediate prognosis* This brings up the crucial question in cerebral thrombosis Where does the patient stand in the stroke process when he is first examined? Is worsening to be anticipated or not? No rules have yet been laid down which allow one to predict the course A mild paralysis today may become a disastrous hemiplegia tomorrow or the patient s condition may only worsen temporarily for a day or two In basilar artery occlusion dizziness and dysphagia may progress in a few days to total paralysis and deep coma The course of the deficit is so often progressive that a pessimistic attitude on the part of the physician is justified in what appears to be a mild case Extension of the thrombotic process is frequently mentioned as the cause of the progressive course of some strokes and this is probably true in some patients especially if there is involvement of the basilar artery Also in the carotid system thrombus at times propagates from the region in the neck where it started to the more distal suprachnoid portion and possibly into the anterior cerebral artery hindering anastomotic flow from the opposite side Or in middle cerebral occlusion retrograde thrombosis may occur back to the mouth of the anterior cerebral perhaps secondarily infarcting the territory of that vessel In many patients however extension of the thrombus is probably not the cause of the progression of the stroke and some of the ischemia modifying factors already referred to must be held responsible

Many other factors also contribute to the *immediate prognosis* in cerebral thrombosis In the case of large infarcts swelling of the infarcted tissue occurs tentorial herniation follows and the patient dies in 2 to 4 days On the other hand milder degrees of swelling and increased intracranial pressure though causing an apparent progression for 2 to 3 days may not prove fatal In extensive basilar infarction associated with deep coma the patient seldom lives for more than a few days If coma or stupor is present in a case from the beginning survival may be largely determined by the success in keeping the airways clear and maintaining fluid and electrolyte balance (see Chap 272) Respiratory and urinary infections are a constant danger and once they begin there is usually a rapid decline in the patient s condition coincident with the rise in temperature

As for the *eventual or long term prognosis* of the neurologic deficit caused by the stroke there are too many possibilities to recount them in detail In the case of small infarcts recovery may start within hours or a day or two and restoration may be complete In other cases there may be no significant recovery whatsoever and after months of assiduous efforts at rehabilitation the patient may remain bereft of speech with the upper extremity still totally useless and the lower extremity serving only as an uncertain prop in attempting to walk Between these two extremes there is every shade of recovery It is safe to say that the longer the delay before movement begins the poorer the prognosis becomes If recovery is not well started within 1 to 2 weeks the outlook is gloomy both for motor activity and speech and in general it may be said that whatever motor paralysis remains after 5 to 6 months will probably be permanent Sensory improvement has been detected for up to 2 years A hemianopia which has not cleared up in a few weeks will often remain permanently although reading color discrimination and object recognition may continue to improve Lateral medullary infarction might be regarded as an exception to the above rule for difficulty in swallowing may be protracted (4 to 7 weeks) and yet relatively normal function may be restored finally

The question of recovery after cerebral lesions raises the broad problem of the functional substitution of one part of the brain for another At present it is the consensus of opinion that one region does not take over the function of another unless those parts normally worked in close cooperation For example musculature which is subserved by both hemispheres e g the face eyes throat etc may resume functionally normal activity after an extensive hemispheral lesion It has not been proved that recovery from expressive or receptive asphasia is due to the assumption of speech function by the intact nondominant cerebral hemisphere since some part of the damaged speech areas will usually have escaped destruction

Characteristically the paralyzed muscles are flaccid in the first days or weeks following a stroke but gradually spasticity develops and the tendon reflexes become brisker The arm tends to assume a flexed adducted posture whereas the leg is usually extended and adducted Function is rarely if ever restored after the slow [illegible]

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The use of anticoagulant drugs makes an accurate clinical diagnosis imperative Intracranial hemorrhage must be ruled out by relying primarily on examination of the cerebrospinal fluid it is to be remembered however that finding the fluid clear does not necessarily exclude hemorrhage (see p 1594) A control prothrombin concentration and coagulation time are desirable before therapy is started but if this is not feasible the initial doses of anticoagulant drugs can usually be given safely if there is no evidence of active bleeding anywhere in the body The question of whether or not severe hypertension is a contraindication to anticoagulant therapy has not been accurately answered There is no reliable evidence that complications are more frequent in the presence of hypertension and therefore the authors have not withheld anticoagulant therapy in these patients however when the diastolic blood pressure is in the range of 130 mm Hg or more an attempt is made at the same time to lower the pressure gradually with hypotensive agents exercising great care not to prejudice further the circulation in the region of the infarct by too great a reduction in the systemic pressure It would be preferable to avoid reduction of the blood pressure in the 2 week period immediately following a thrombotic stroke

Anticoagulant therapy is safe provided the prothrombin concentration is determined regularly (once a day for the first 10 days thence thrice a week and finally every week or 10 days) at a laboratory using reliable methods Therapy can be prolonged for months and years and only occasionally is it necessary to interrupt treatment because of unexplained disturbances of coagulation Dicumarol overdosage will cause hemorrhage from the kidney nose bowel skin or into muscle Although these accidents are usually not serious vitamin K_1 should be administered immediately

Prevention of a Stroke by Avoiding Situations in Which Strokes Are Likely to Occur (1) Particular care should be taken to maintain the systemic blood pressure oxygenation and intracranial blood flow during surgical procedures especially in elderly patients (2) hypotensive agents whether given therapeutically or for diagnostic procedures should be administered with great care (3) in the elderly patient in whom deep sleep might help to precipitate cerebral ischemia oversedation should be avoided (4) systemic hypotension severe anemia and polycythemia should be treated promptly

GENERAL The methods just discussed for the most part constitute delaying actions The ultimate solution of the problem lies in more fundamental fields Atherosclerosis and hypertension must be prevented or alleviated (see Chap 228 for prophylaxis of atherosclerosis and Chap 227 for the treatment of hypertension) Another factor possibly of great importance in contributing to vascular disease is the smoking of cigarettes the authors advise all patients with cerebral atherothrombotic disease to stop smoking Hypercoagulability of the blood has been suggested as the explanation for the fact that some atherosclerotic patients are more disposed to thrombotic episodes than others Correction of such an abnormality would be highly advantageous but at present there is no reliable method of detecting intravascular hypercoagulability if such a disorder exists

CEREBRAL EMBOLISM

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up from his bed particularly in the morning or postoperatively. In the upright posture the cerebral circulation falls, and for this reason it is recommended that patients with a stroke as the result of ischemic infarction should remain horizontal in bed for 7 to 10 days initially, and that when ambulation starts special attention should be given to preservation of the systemic circulation (the patient must avoid standing quietly for prolonged periods, must sit with the feet up, etc.). In stroke cases it is of great importance that the systemic blood pressure be maintained (correction of blood loss, use of Levophed in myocardial infarction with vascular collapse, avoidance of autonomic blocking agents, etc.). Injections of epinephrine have been recommended as a means of raising the systemic blood pressure above the usual levels. Although this enhances cerebral blood flow and could be beneficial, a systematic trial in thrombotic cases has not been undertaken. Anemia must be corrected. (4) Recently a few surgeons have undertaken to relieve arterial obstruction surgically. The procedures used include carotid thromboendarterectomy, resection of the carotid bifurcation with either insertion of a graft or a direct end-to-end anastomosis, arterial loop grafts to bypass an occluded portion of the carotid artery, and embolectomy. Some of these operations were performed in cases in which a stroke had recently developed; in others, they were carried out because of prodromal transient ischemic attacks. It has been impossible to evaluate the results. The operations themselves carry considerable risk.

Physical Therapy and Rehabilitation. Beginning within a few days, the joints of the paralyzed limbs should be passively carried through a full range of movement twenty to fifty times a day. Contracture shortening must be avoided, especially at the shoulder, elbows and ankle. Pain, soreness and aching in the paralyzed limbs may temporarily interfere with exercises. The patient can be placed in a chair after 2 weeks or so, depending on the severity of his illness. Nearly all hemiplegics can learn to walk again to some extent, usually within a 3- to 6-month period, and this should be a primary aim in rehabilitation. A long or short leg brace is often required. Speech therapy is of questionable value but should be tried. At least it is of value psychologically. Physical therapy seems not to benefit patients with cerebellar ataxia. As the hemiplegic patient improves and if mentality is preserved, instruction in the activities of daily living, using various special devices, can assist him in becoming at least partially independent in the home.

Preventive Measures against Strokes and Vascular Disease. Once a thrombotic stroke has developed fully, no therapy so far devised is of any value in restoring function. There is no need to emphasize the fact that prevention is the most important category of therapy. Preventive measures in cerebral thrombosis might be divided into special and *general*.

SPECIAL. *Prevention of a Thrombotic Stroke of Which There Has Been a Warning in the Form of One or More Transient Ischemic Attacks.* Many different therapies have been recommended: papaverine and phenobarbital, cervical sympathectomy, nicotinic acid, aminophylline, and breathing 5 per cent carbon dioxide in oxygen. However, each of these methods has failed in the hands of other workers. According to first reports, anticoagulant therapy promises both to prevent the ischemic episodes and to postpone indefinitely the arrival of an impending stroke, whether the carotid or basilar system is involved. However, further studies are necessary before anticoagulant therapy can be unequivocally recommended. Recently surgical procedures—carotid endarterectomy or carotid resection—have been undertaken in order to restore the cerebral circulation and prevent ischemic attacks. To date it has been impossible to evaluate the results.

Halting the Advance of a Progressive Thrombotic Stroke. This problem is closely allied to that just discussed and refers to strokes which are evolving in a stepwise fashion. Nicotinic acid, stellate block, and 5 per cent CO_2 inhalation are ineffective. At present, anticoagulant therapy seems to be the most effective measure, but is not successful in all cases. In trying to decide whether or not anticoagulant therapy is indicated, one faces again the crucial question in thrombotic strokes: Where in the course of his stroke does the patient stand when he is first examined? Will his course be benign or disastrous? Unfortunately no answers have yet been formulated.

Prevention of Repeated Strokes. Not infrequently one encounters patients in whom several separate, usually small, thrombotic strokes occur within a period of several months. Hypertension is usually present. Thus far anticoagulant therapy is the only measure recommended for the prevention of these recurrences, but its value has yet to be assessed (see Cerebral Embolism, p. 1558).

When *anticoagulant therapy* is instituted in stroke cases, Dicumarol or a drug of similar action is usually used. If an anticoagulant effect appears to be urgently required, heparin is administered concomitantly intravenously in doses of 50 to 75 mg every 3 to 5 hr until the Dicumarol becomes effective. Heparin can also be injected deep-subcutaneously in a dosage of approximately 100 mg every 6 to 9 hr as determined by coagulation tests. Dicumarol alone is sufficient in patients with transient ischemic attacks, repeated thrombotic strokes, or cerebral embolism (see p. 1558). [illegible]

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to explain the infarct the absence of atherosclerosis or other cause for thrombosis in the cerebral vessel a ready source of embolus infarcts in other organs such as kidney and spleen the occurrence of hemorrhagic infarction and last but not least the clinical history

Because of the rapidity with which emboli cause occlusion there usually is not time for collateral *influx to become established* Thus sparing of territory distal to the site of occlusion is not so common as in thrombosis However all the ischemia modifying factors mentioned under thrombosis are still operative and will influence the size shape and severity of the infarct

Brain embolism is essentially a manifestation of heart disease Many kinds of heart disease can be associated with embolism The commonest direct cause is *chronic atrial fibrillation* due to atherosclerotic or rheumatic heart disease the source of the embolus being mural thrombus deposited within the auricular appendage Atrial fibrillation due to other types of heart disease can of course also lead to embolism e g hypertensive congenital thyrotoxic syphilitic etc Embolism probably occurs also *during paroxysmal auricular fibrillation or flutter* but there is need for further exact documentation of such cases Mural thrombus deposited on the damaged endocardium overlying a myocardial infarct is the second most frequent source of cerebral emboli Emboli can also arise from atrial thrombus associated with severe mitral stenosis without atrial fibrillation Cardiac surgery especially valvoplasty may disseminate fragments of thrombus or particles of a calcified valve leaflet Subendocardial fibroelastosis idiopathic myocardial hypertrophy and cardiac tumors are rare causes of embolism

The vegetations of acute and subacute bacterial endocarditis being infected give rise to septic embolism which results in several different pathologic pictures in the brain In some cases the infarcts (they are usually multiple) do not differ from those due to uninfected emboli but in others tiny septic infarcts develop or in the case of acute bacterial endocarditis there may be miliary abscesses into which a small amount of hemorrhage may occur (focal embolic encephalitis) Mycotic aneurysm now seen infrequently is another complication of septic embolism and may be a source of intracerebral or subarachnoid hemorrhage

Marantic or nonbacterial endocarditis occasionally causes cerebral embolism and can produce a most baffling clinical picture especially when associated as it often is with carcinomatosis Paradoxic embolism can occur when an abnormal communication exists between the right and left sides of the heart or when both ventricles communicate with the aorta Thus embolic material arising in the veins of the lower extremity or indeed anywhere in the systemic venous tree can bypass the pulmonary circulation and reach the cerebral vessels

Other sources of embolic material are far less frequent (1) Mural thrombus deposited upon ulcerated atheroma in the arch of the aorta or in the carotid arteries may break loose and find its way into brain arteries A large plaque of atherosclerosis is frequently present in the carotid sinus and massage of the carotid sinus may dislodge mural thrombus deposited thereon with the production of a hemiplegia This is one of the reasons why carotid massage should always be carried out gently (2) Atheromatous material may be washed out of a large plaque in the aorta or carotid vessels and carried distally into the branches of the affected vessel (3) The pulmonary veins are a source of cerebral emboli as indicated by the occurrence of cerebral abscesses in association with pulmonary suppurative processes and by the high incidence of carcinoma of the brain secondary to pulmonary deposits (4) Surgery of the neck and thorax can be complicated by cerebral embolism A rare type is that which follows thyroidectomy in which thrombosis in the stump of the superior thyroid artery *extends proximally until a section of it protruding* into the lumen of the carotid is carried away into the cerebral arteries

Cerebral embolism must have occurred in every case in which secondary tumor is deposited in the brain likewise cerebral embolism must regularly accompany septicemia Rarely is the mass of tumor cells or bacteria large enough to occlude a cerebral artery and produce the picture of a stroke Nevertheless tumor embolism has been reported secondary to cardiac myomyxomas and occasionally with other tumors Embolism in the course of septicemia usually means that a vegetative endocarditis is present with thrombus formation Cerebral fat embolism is usually related to trauma As a rule the emboli are minute and widely dispersed and accordingly the clinical picture is usually not focal, as in strokes Cerebral air embolism is a rare complication of criminal abortion or of cervical and thoracic operations and was formerly encountered as a complication of pneumothorax therapy

Not infrequently at autopsy the diagnosis of cerebral embolism is made with full justification without finding a source The same is true of embolism elsewhere in the body Possibly the routine search for a thrombotic nidus is not sufficiently thorough and small thrombi in the auricular appendage the pulmonary veins or the endocardium between the papillary muscles of the heart may be overlooked Nevertheless in some cases studied most carefully no source of embolic material has been discovered

The Clinical Picture Of all strokes those due to cerebral embolism develop most rapidly Like a

bolt from the blue" the full blown picture evolves within several seconds or a minute exemplifying most strikingly the temporal profile of a stroke The clinical picture comes in a single sudden attack scarcely ever in stuttering fashion As a rule there are no warning episodes whatsoever These statements are possibly too stringent for in occasional cases the picture may take several hours to develop or a transient episode may precede the final arrival of the stroke However any emphasis on these few exceptions is entirely misleading The embolus strikes at any time of the day or night When the stroke develops during sleep its exact mode of development will not be known

The neurologic picture will depend on the artery blocked and where along its course the obstruction lies The syndromes related to each cerebrovascular territory are the same as those outlined under thrombosis (see p 1565 ff) A large embolus may plug the internal carotid artery or the stem of the middle cerebral artery producing a severe hemiplegia Or the embolus may be smaller and pass into one of the branches of the middle cerebral artery and produce a strikingly focal disorder motor aphasia a monoplegia (or part thereof) a receptive type of aphasia with little or no motor paralysis or a sensorimotor paralysis with little or no involvement of the supersensory zone It is important to realize that an embolus in its passage along an artery may temporarily compromise the local circulation with the production of a severe neurologic deficit which clears up almost as quickly as it came because the embolus finally passes into a branch supplying a relatively silent part of the hemisphere In other word embolism is one of the causes (and not an uncommon one) for a single evanescent stroke Embolic material entering the vertebral basilar system occasionally lodges in the vertebral artery just below its union with the basilar but more often the embolus traverses the vertebral and since the basilar artery is larger than the vertebral the embolus will not be held up until it reaches the upper bifurcation of the basilar artery If arrested here it abruptly produces deep coma and total paralysis More often the embolus enters one or the other posterior cerebral artery or both of them and by infarcting the visual cortex causes a unilateral or bilateral homonymous hemianopia It is rare for embolic material to enter the pontine vessels whereas embolic infarction of the under surface of the cerebellum is extremely common It has already been pointed out that recurrent transient ischemic attacks of the same pattern are not likely to be embolic since successive emboli could not be expected to lodge at identical sites

The more general neurologic disturbance associated with embolic strokes is not significantly different from that seen in thrombotic cases and the reader is referred to the description of the changes in consciousness respiration etc on p 1564 Again the patient may have a most devastating hemiplegia and yet be quite alert Headache is not uncommon

Although the abruptness with which the stroke develops and the lack of prodromal symptoms point strongly to embolism it is the total clinical picture upon which the diagnosis is based If hemorrhage is ruled out there remains only thrombosis to be excluded The presence of auricular fibrillation a history of myocardial infarction (recent or in the preceding months) or the occurrence of embolism to other regions of the body all support the diagnosis of embolism Embolism merits the most careful consideration in young persons in whom atherosclerosis is rather unlikely Not infrequently the first sign of myocardial infarction is the occurrence of embolism and therefore it is advised that an electrocardiogram be made in all cerebrovascular strokes of uncertain origin

Acute and subacute bacterial endocarditis do not usually present as a stroke due to infarction although this does happen occasionally The clinical signs of endocarditis anemia splenomegaly and often a pleocytosis in the cerebrospinal fluid should point to the correct diagnosis

The diagnosis of the other causes of cerebral embolism—cardiac surgery neck surgery pulmonary vein thrombosis marantic endocarditis paradoxic embolism tumor fat and air—will not be enlarged upon here

Laboratory Findings The description under thrombosis (p 1581) applies for the most part to embolism except in so far as hemorrhagic infarction and septic embolism (focal embolic encephalitis) are concerned Cerebral embolism commonly produces hemorrhagic infarction which in most instances does not cause the cerebrospinal fluid to be bloody However in some excessively hemorrhagic infarcts the fluid may be grossly bloody and contain as high as 10 000 or more red cells per cubic millimeter The pressure is relatively normal and this may help to distinguish the process from primary intracerebral hemorrhage In the milder cases of hemorrhagic infarction a slight xanthochromia (grade 1 to 2 on the scale of 1 to 10) may appear after a few days The possibility that embolic infarcts are unusually bloody indicates the danger of administering anticoagulants routinely in cases of cerebral embolism Also it necessitates caution in assuming that blood in the spinal fluid is unequivocal evidence that the stroke is due primarily to a hemorrhage

In the septic embolism of subacute bacterial endocarditis the white blood cells in the cerebrospinal fluid may number as high as several hundred but are usually less than 200 per cubic millimeter the proportion of lymphocytes and polymorphonu

clears varying with the acuteness of the septic process There may also be several hundred or more red blood cells and a faint xanthochromia is often present However a pleocytosis is not invariably seen in this condition The protein values are elevated and the sugar content is within normal limits No bacteria are seen or obtained by culture In acute bacterial endocarditis there may be either a frank purulent meningitis or the cerebrospinal fluid formula of subacute endocarditis

Course and Prognosis The remarks made concerning the *immediate prognosis* in cerebral thrombosis apply as well here Life is threatened in patients who have massive cerebral swelling made quite airway and respiratory or urinary infection As a rule all but the most aggravated cases survive the initial insult Massive brain stem infarction as a result of basilar embolism is almost always fatal The *eventual prognosis* as to survival is determined by the occurrence of further emboli and the gravity of the underlying illness cardiac failure rheumatic heart disease myocardial infarction bacterial endocarditis malignant growth etc The threat of an early recurrence of embolism is very real and it is not uncommon to have the second embolus strike within a few days or weeks of the first The urgency of anticoagulant therapy is thereby underlined The *eventual prognosis* regarding the neurologic deficit is not different from that given for cerebral thrombosis (p 1582) The fact that an embolic episode may last only minutes or hours before clearing up is to be emphasized especially in estimating the effect of any therapeutic measure

Treatment The first three phases of therapy—(1) general medical management in the acute phase (2) measures directed to restoring the integrity of damaged tissue and (3) rehabilitation—are the same as described under cerebral thrombosis (see p 1583) Occasional attempts at embolectomy from the middle cerebral artery have been made but unsuccessfully In the field of prophylaxis there is strong evidence that the use of long term anticoagulant therapy is effective in the prevention of embolism in cases of auricular fibrillation and myocardial infarction After cerebral embolism has occurred the question arises as to the necessity of delaying anticoagulant therapy for several days to avoid precipitating bleeding into a hemorrhagic infarct It is the authors practice always to perform a lumbar puncture first in order to rule out gross hemorrhage from the infarct If the cerebrospinal fluid is clear (this does not rule out a hemorrhagic infarct) the authors proceed with anticoagulant therapy since there is the constant danger of another embolus breaking away from the heart The authors have not encountered a case in which the use of anticoagulant drugs has seemed to increase the degree of hemorrhage within a hemorrhagic infarct indicating that such therapy is relatively safe Rare exceptions to this statement may be expected The use of anticoagulant therapy in cases of acute myocardial infarction including those judged to be in the "good risk" category is advisable In cerebral embolism associated with subacute bacterial endocarditis anticoagulant therapy is usually held to be contraindicated because of the danger of intracranial bleeding but this viewpoint is based on flimsy evidence Nevertheless caution is advisable in this matter and it is preferable to rely on a rapid sterilization of the blood stream

Valvoplasty and amputation of the auricular appendage have substantially reduced the incidence of embolism in rheumatic heart disease The need for special care in preventing emboli from entering the carotid arteries during the performance of cardiac valvoplasty is appreciated by all thoracic surgeons

OTHER CAUSES OF CEREBRAL INFARCTION

Reference to the classification IC will show that there are only a few causes of cerebral thrombosis other than atherosclerosis and fewer still that are important in the stroke picture *Venous thrombosis* (considered under VII) is a rather uncommon condition and rarely mimics a cerebrovascular stroke Arising in relation to extracranial and intracranial sepsis surgical operations parturition and chronic wasting illnesses particularly in children it can cause a relatively mild neurologic illness with raised intracranial pressure headache visual obscurations and focal seizures or on the other hand it can lead to extensive cerebral infarction and hemorrhage with grave neurologic manifestations

Systemic hypotension usually results in unconsciousness (syncope) without focal motor and sensory signs but in the presence of vascular narrowing from any cause weakness or numbness may be precipitated and if the state of vascular collapse persists for a sufficient length of time local infarction will occur distal to the point of stenosis It has already been mentioned that transient ischemic attacks and persistent strokes often develop under circumstances which suggest that a fall of the systemic blood pressure was the precipitating factor Hypotension occurs in simple faint acute blood loss myocardial infarction Stokes Adams syndrome traumatic and surgical shock cardiac arrest or anesthetic accident during surgery hypersensitivity of the carotid sinus reflex and in the several types of postural hypotension (idiopathic postsympathectomy tabetic diabetic with autonomic blocking agents with Serpasil and on getting up and around after surgical operations)

Arteriography occasionally results in cerebral infarction In some cases this is because of cerebral thrombosis but the pathogenesis of other cases requires further study *Arteritis* is no longer a common cause of cerebral thrombosis at least in North America owing to the present satisfactory treatment of syphilis This is to be contrasted with the period up to 10 years ago when meningovascular syphilis had to be seriously considered in every stroke case "hemiplegia in the young" especially was strongly indicative of syphilis Necrotizing or granulomatous arteritis whether limited to the cerebral vessels or occurring as part of a polyarteritis has usually produced a slowly progressive neurologic deficit and has only rarely mimicked a stroke Idiopathic giant cell arteritis involving the large arteries arising from the aortic arch is a rare cause of unilateral or bilateral carotid occlusion but must be kept in mind It appears to be much more common in young women in Japan the aforementioned Takayasu s syndrome or "pulseless disease Cranial arteritis or temporal arteritis is almost always limited to the extracranial arteries except for the small vessels supplying the optic and oculomotor nerves Unfortunately in over 50 per cent of cases permanent blindness or a severe impairment of vision results When the process has involved the internal or common carotid arteries it has usually not caused a stroke (see p 1708 Chap 264)

Polycythemia sickle-cell disease and *thrombotic thrombopenia* are stated to be causes of cerebral thrombosis but further study of the matter is required A *dissecting aortic aneurysm* may involve the large vessels arising from the arch and result in carotid occlusion and hemiplegia a concomitant fall in systemic blood pressure probably contributing to the picture *Carotid occlusion* may be the result of direct *trauma* to the neck or it may be precipitated by a "closed head injury sometimes of a seemingly trivial nature *Hypoxia* usually produces a diffuse destruction of neurones rather than frank infarction but bilateral softening of the globus pallidus is a classical feature *Tentorial and subfalcial herniation* and sometimes cerebellar pressure can cause infarction by compression of the posterior and anterior cerebral and inferior cerebellar arteries respectively Under the rare types of infarction it should be mentioned that carotid occlusion has been described following *tonsillectomy* in association with *cavernous sinus thrombophlebitis* and the *trigeminal ganglionitis of herpes zoster* Also a previously transient and harmless migrainous aura is occasionally transformed into a persistent deficit presumably because of infarction as the result of excessive ischemia This complication most frequently takes the form of a homonymous hemianopia Finally a category for *cerebral infarction of undetermined cause* is included for it must be admitted that in some cases even at neuropathologic examination it is impossible to determine the exact cause of an infarct

Omitted from the classification is *Binswanger s chronic progressive subcortical encephalitis* a rare disease of cerebral white matter tentatively attributed by Binswanger to atherosclerosis The status of the disease is uncertain at present, and further investigation of the problem is warranted before the disease can be accepted as a separate entity

RECURRENT FOCAL CEREBRAL ISCHEMIA

It has already been pointed out that when transient ischemic attacks precede a stroke they stamp the process as thrombotic Furthermore neuropathologic studies indicate that these attacks are linked almost exclusively to atherosclerotic thrombosis although further data on this point are desirable They belong therefore under the heading of cerebral thrombosis but a separate category has been formed for them because of their importance clinically and therapeutically Recurrent ischemic cerebral attacks consist of recurrent transient episodes of focal cerebral disturbance e g weakness numbness dizziness etc and are most commonly encountered in the days or weeks preceding the onset of a thrombotic stroke occurring as a sort of a warning that disaster threatens In recent years increasing attention has been directed to these attacks with the purpose of preventing the arrival of the threatening stroke by administering anticoagulant drugs at the stage of prodromal symptoms There would seem to be little doubt that they are due to transient focal ischemia and they might be referred to as temporary strokes which fortunately reverse themselves Corresponding to the higher incidence of atherosclerosis in hypertension and in the male population about two-thirds of all patients with transient ischemic attacks are men and/or hypertensive

The Clinical Picture Transient ischemic attacks can occur by themselves or they may precede accompany or follow the development of a stroke So far it has not been possible to distinguish the early cases destined to do well from those in which a full blown stroke will develop Thrombosis of virtually any cerebral or cerebellar artery deep or superficial can be associated with transient ischemic attacks e g common carotid internal carotid middle cerebral anterior cerebral ophthalmic vertebral, basilar posterior cerebral the cerebellar arteries and the penetrating branches to the deep structures of the basal ganglions and brain stem If the posterior cerebral arteries are included in the vertebral basilar system ischemic episodes are

slightly more common in that system than in the carotid system

The neurologic features of the transient episode indicate the territory or artery involved and are fragments borrowed from the stroke which often is approaching. In the carotid system the episodes commonly take the form of unilateral weakness or numbness of the side of the body opposite the lesion. The entire side may be involved or the parts in various combinations face and lips or lips and fingers fingers alone hand and foot etc. Other manifestations include aphasia difficulty in calculation and other temporal parietal occipital functions (when the dominant hemisphere is involved) confusion veering to one side transient monocular blindness or blurring of vision scintillating scotomas headache and possibly focal epileptic seizures. Lack of pulsation in the carotid artery in the neck or pharynx reduced pressure in the appropriate central retinal artery and a contralateral cranial bruit indicate carotid occlusion

The clinical picture in the vertebral basilar system is exceedingly diverse since so much motor and sensory traffic is sustained by the blood carried in these vessels. Occurring in the most varied combinations the following manifestations may be recognized (the more common ones are italicized) *weakness* of part or all of one side of the body or both sides *numbness* of part or all of one side or both sides or crossed numbness (one side of face and opposite limbs) *dizziness diplopia* (vertical or horizontal) dark vision *blurred vision* tunnel vision partial or complete blindness scintillating scotomas pupillary change ptosis paralysis of gaze *dysarthria speechlessness dysphagia staggering gait* veering to one side *headache* noise or pounding in the ear or in the head head or face pain peculiar head sensations vomiting hiccoughing memory lapse confused behavior drowsiness unconsciousness (rare) impaired hearing deafness a feeling of movement of a part sweating and facial redness

It is not always easy to identify the territory affected. However the occurrence of receptive or sensory aphasia always points to the carotid system as does monocular blindness with or without contralateral numbness or weakness. The hallmarks of vertebral basilar involvement are (1) bilateral weakness and/or numbness i e a disturbance of the long motor or sensory tracts bilaterally (2) involvement of the infranuclear portion of one or more cranial nerves (3) disturbance of other segmental structures i e posture equilibrium ocular and visceral mechanisms. Perioral numbness is a not infrequent complaint and the patient often is not certain whether it is equally bilateral bilateral with unilateral preponderance or mostly unilateral with spread slightly to the other side of the midline. Diplopia and whirling dizziness are of particular importance in localization for they are rarely if ever associated with occlusion of the carotid system. Unilateral weakness and unilateral numbness as isolated phenomena are difficult to localize since they can occur in both carotid and basilar occlusion

The following manifestations are either very rare or may not occur at all in ischemic attacks unconsciousness convulsive movements fecal or urinary incontinence facial pallor formed hallucinations and the manifestations of temporal lobe seizures

Transient ischemic attacks last from a few seconds up to several hours the most common duration being a few seconds up to 5 to 10 min. It is uncommon for recurrent discrete attacks to last more *than 30 min. There may be only a few attacks or* several hundred. Between attacks the neurologic examination may disclose no abnormalities. A stroke may ensue after the second episode or may be postponed until hundreds have occurred over a period of weeks or months. Not infrequently the attacks gradually cease and no important paralysis occurs a fact which makes any form of therapy difficult to evaluate. The attacks may all take ap*proximately the same pattern or they may* vary considerably in detail although maintaining the same basic pattern. For example weakness or numbness may involve fingers and face in some episodes and fingers only in others or dizziness alone may occur in some attacks while in others diplopia is added to the picture. In basilar artery disease each side of the body may be affected alternately. All the involved parts may be affected simultaneously or a definite march or spread from one region to another can occur in a period of 10 to 60 sec or even as long as several minutes e g numbness may spread from the hand to the face or the reverse. The attacks may cease abruptly or fade gradually

The onset of attacks in some patients is clearly related to standing up after lying or sitting. In general attacks are likely to occur when the patient is up and around rather than lying down but in many cases the episodes bear no relation to position or activity. They have been encountered in relation to exercise exertion emotional outbursts of anger or joy and during bouts of coughing. Transient symptoms present on awakening from sleep usually indicate that a stroke is in the offing

Ophthalmoscopic observations of the retinal vessels made during episodes of transient monocular blindness show arrest of the blood flow in the retinal arteries and breaking up of the venous column to *form the well known box car pattern*. This could well indicate that in ischemic attacks elsewhere a temporary complete or relatively complete cessation of blood flow occurs locally

The pathogenesis of transient ischemic attacks is still not clear. In the past they have been attributed

to cerebral vasospasm or to transient episodes of systemic arterial hypotension with resulting compromise of the intracranial circulation Neither of these factors has been established Although dropping the blood pressure to 90 or even 80 mm Hg by tilting the patient on a tilt table into an upright position may cause EEG changes it has not in the authors experience reproduced the attacks Vasodilator drugs have been without effect There is increasing evidence that the attacks are abolished by anticoagulant drugs but the mechanism of this is not known Whatever their exact cause they are closely related to vascular occlusion due to thrombosis A proper recognition of the transient ischemic episode is of importance since the use of anticoagulant drugs may prove of value in warding off an oncoming stroke

The differential diagnosis of recurrent cerebral ischemic attacks raises special problems The following conditions must be differentiated cerebral seizures (epileptic seizures) Menieres syndrome paralytic migraine Stokes Adams attacks hypersensitive carotid sinus reflex akinetic falling spells of the aged and recurrent cerebral embolism

Frank motor convulsions rarely if ever occur in ischemic attacks The patient may report a feeling of movement distortion or drawing but jerking or twitching has not been encountered On the other hand a cerebral seizure rarely if ever displays as its only manifestation a temporary paralysis of a limb or of one side of the body Unconsciousness *is rare in ischemic attacks and its occurrence even* in only a few attacks indicates a seizure phenomenon Incontinence of bowel and bladder tongue biting cyanosis and residual sleepiness or muscle soreness are indicative of a seizure rather than an ischemic episode In the sensory sphere the distinction between ischemic episodes and seizures is less clear for numbness or scintillating visual phenomena are seen in both conditions and therefore the presence of associated phenomena (dizziness diplopia etc) must be relied on in making a differentiation When numbness appears simultaneously in face hand and leg i e when there is no march ischemia rather than a seizure is probably responsible When a *sensory march* occurs it will not serve to distinguish the two for while it is more characteristic of a seizure it may also occur *in ischemic episodes However in the latter its* spread is often slower in terms of minutes rather than seconds

The type of dizziness associated with brain stem ischemia has no characteristics which allow it to be distinguished from that seen in Menieres syndrome or labyrinthitis Therefore in making a diagnosis one depends on the presence of certain associated symptoms and signs It is a simple matter to decide that the dizziness is of central origin when there are other evidences of brain stem involvement by history or on neurologic examination diplopia numbness weakness dysphagia dysarthria cerebellar ataxia vertical nystagmus persistent horizontal nystagmus etc On the other hand the isolated presence of the triad of recurrent dizziness *tinnitus and chronic deafness (i e signs of both* auditory and vestibular involvement) is almost certain evidence of Menieres syndrome However the pictures at times resemble each other closely and only an especially thorough search will reveal signs indicating that the disorder is due to ischemia of the brain stem Tinnitus of a constant hissing or ringing type is a rare complaint in brain stem vascular disease When dizziness is the sole symptom in an elderly person it is often impossible to make an accurate diagnosis and only after observing the patient for a period of time will the nature of the underlying disease be disclosed Finally it must be remembered that since both basilar artery disease *and Menieres syndrome are common in this age* group the two conditions may coexist

The visual sensory and motor phenomena which precede the headache in some cases of migraine bear a close resemblance to ischemic manifestations but since migraine originates in early life only occasionally does its differentiation from ischemic attacks pose any problem When vascular disease has its onset during the period of life when migraine is prevalent the two may be confused until the history is carefully taken Occasionally a *migrainous paralytic aura returns after a headache* free interval of 10 to 20 years It has already been pointed out that headache at times of great intensity *frequently* accompanies cerebral thrombosis therefore in the elderly person the occurrence for the first time of periodic headache associated with scintillations or numbness should always suggest atherothrombosis rather than migraine *Stokes Adams attacks* and *hypersensitivity* of the *carotid sinus reflex* cause collapsing spells" with unconsciousness confusion and jerking but almost never do they produce focal neurologic manifestations such as numbness weakness diplopia etc Difficulty in differentiation of these conditions will arise only when the clinical details *of the episode are not* available and usually a careful minute by minute description of the attack will enable the correct diagnosis to be reached *Only in an occasional* case of basilar artery insufficiency will an ischemic episode result in unconsciousness usually accompanied by other symptoms such as weakness numbness blindness or dysarthria In *akinetic falling spells of the aged* a rather vague entity the patient falls unconscious without convulsive movements color change or alteration in pulse blood pressure or respiration Within a minute or two consciousness is restored

Cerebral embolism is frequently suggested as an explanation for recurrent cerebrovascular episodes However this seems unlikely if all the attacks are of identical pattern for successive emboli coming from a distance could not be expected to enter the same arterial branch Moreover the involved cerebral tissue would be at least partially damaged leaving some residual signs When only a single transient episode has occurred the factor of recurrence does not assist in the diagnosis and cerebral embolism must then be strongly considered

Treatment The therapy of transient ischemic attacks has already been discussed under cerebral thrombosis (p 1583) where it was pointed out that the administration of anticoagulant drugs usually stops the attacks and prevents indefinitely the onset of a threatening stroke Since in many patients the attacks cease spontaneously it would be desirable to have the indication for anticoagulant therapy more clearly set down However at present it is not possible to predict the course of recurrent ischemia and only tentative directions for anticoagulant therapy can be offered If the attacks are becoming more frequent more severe or of longer duration or if each attack no longer clears away completely and a persistent neurologic deficit is accumulating anticoagulant drugs are indicated When the episodes are few and spaced at long intervals further observation is warranted

Other measures that have been recommended include administration of phenobarbital papaverine or nicotinic acid inhalation of 5 per cent carbon dioxide breathing into a paper bag and stellate block or cervical sympathectomy but none of these has proved effective under careful clinical testing On several occasions the authors have been impressed with the salutary effect of having the patient stop smoking cigarettes For the more general therapeutic measures applicable in these cases see pp 1583 to 1586

HYPERTENSIVE INTRACEREBRAL HEMORRHAGE

Although 12 different causes of intracranial hemorrhage have been listed in the classification the first two hypertensive intracerebral hemorrhage and ruptured saccular aneurysm are much more important than the others and account for most of the hemorrhages which give rise to the clinical picture of a stroke Duret hemorrhages hypertensive encephalopathy and idiopathic brain purpura will not simulate a stroke and are included only for the sake of completeness

Hypertensive intracerebral hemorrhage is the ordinary well recognized brain hemorrhage Generally speaking the higher the blood pressure the more likely it is for hemorrhage to occur and though in some cases the levels are only in the range of 160 to 170/90 in most cases they are much higher The hemorrhage occurs within brain tissue and rupture of the arteries lying in the subarachnoid space is practically unknown apart from aneurysms It is a mistake to think of hypertensive hemorrhage as arising from the large arteries at the base of the brain The extravasation which results from rupture of an artery forms a roughly circular or oval mass which grows in volume as the bleeding continues Adjacent brain tissue is displaced and compressed If the hemorrhage is large midline structures are shifted to the opposite side and vital centers are compromised leading to coma and death Rupture or seepage into the ventricular system usually occurs and the spinal fluid becomes bloody in more than 90 per cent of cases A hemorrhage of this type almost never ruptures directly into the subarachnoid space through the cortex When the hemorrhage is small and placed at a distance from the ventricles the cerebrospinal fluid may remain clear even on repeated examinations

In order of frequency the commonest sites for hemorrhage are (1) the putamen and adjacent internal capsule (40 per cent of cases) (2) thalamus (3) cerebellar hemisphere (4) pons and (5) various parts of the central white matter (frontal lobe corona radiata etc) The vessel involved is usually a small penetrating artery The nature of the vascular lesion which leads to arterial rupture is not known and indeed the site of the rupture has not often been identified Atherosclerosis is held by many to be a factor but there is no proof for this view and hemorrhages are encountered in the absence of grossly visible atherosclerosis Small aneurysmal dilatations were reported by Charcot and Bouchard to be the basis for the rupture They may be responsible for hemorrhage in some instances but their occurrence only in arterioles and frequently in the cerebral cortex makes it unlikely that they explain many of the massive cerebral hemorrhages Hyalinosis of the small arteries due to hypertension has also been described as the precursor of hemorrhage Another hypothesis attributes the hemorrhage to a confluence of myriads of smaller diapedetic hemorrhages rather than a single extravasation but this is entirely without grounds and represents a confusion of hemorrhagic infarction and massive hemorrhage

Hemorrhages might be classified as massive small slit and petechial "Massive" refers to huge hemorrhages several centimeters in diameter "small" to those 1 to 2 cm in diameter slit applies to a special type of hypertensive hemorrhage which lies subcortically at the junction of white and gray matter and which in the healing stage becomes narrowed to an orange slit

The Clinical Picture The clinical picture conforms accurately *to the temporal profile of a cerebrovascular stroke* viz it has an abrupt onset and rather rapid evolution The stroke usually evolves *with gradualness* (not so suddenly as in embolism) taking minutes hours or occasionally days (average of 1 to 6 hr) to reach its peak depending on the speed of bleeding As a rule there are no recognizable warning or prodromal symptoms the patient being stricken out of the blue" Often the patient has been astonishingly well and headache dizziness and epistaxis have not occurred with any consistency as prodromal symptoms In the great majority of cases the hemorrhage comes on while the patient is up and active and onset during sleep is a great rarity Hypertension is by definition always present and the elevation is maintained early in the course of the stroke or may even rise higher so that the existence of hypertension will be easily established when the patient is first examined There is usually only one episode of hemorrhage and recurrent episodes of bleeding from the same site such as occur in cases of saccular aneurysm are not encountered Once bleeding has become arrested rebleeding in the near future that is after the first few days is not to be anticipated The neurologic deficit is never transitory in intracerebral hemorrhage as it so often is in thrombosis and embolism Once blood is spilled into the tissues it is removed only slowly over a period of weeks and months during which time symptoms and signs persist For the same reason rapid fluctuations in the neurologic deficit from one examination to another are not to be expected Cerebral seizures focal or generalized are not so rare at the onset of hemorrhage as at the onset of infarction and occur in the first few days in about 10 per cent of cases (not including attacks of "decerebrate rigidity")

The neurologic signs and symptoms vary with the site and size of the extravasation The commonest picture is that associated with a putaminal or thalamic hemorrhage in which the adjacent internal capsule is implicated The patient suddenly complains of something going awry within the head In a few minutes the face sags on one side speech becomes slurred or aphasic the arm and leg gradually weaken and the eyes tend to deviate away from the side of the paretic limbs A carefully taken history often reveals that these events occurred gradually over a period of 5 to 30 min This type of evolution is virtually diagnostic of intracerebral bleeding Gradually the paralysis worsens the affected limbs become flaccid pinprick is not appreciated a Babinski sign appears speaking becomes impossible and confusion gives way to stupor In the worst cases when blood enters the ventricular system under high pressure coma supervenes There is then a Babinski sign bilaterally respirations become labored deep irregular or intermittent *extensor rigidity occurs the pupils dilate and the* patient dies within a period varying from a few hours up to 24 or 48 hr This unfortunately is the course in over half the cases Respiratory failure nearly always precedes circulatory failure just as it does with all diseases of the brain but late in the course the blood pressure may fall A stroke is rarely the cause of sudden death unless it accompanies cardiac or respiratory disease However not all hemorrhages prove fatal and at any point bleeding may stop and if vital structures have not been irreversibly damaged the patient will survive (15 to 30 per cent of cases) The patients who do not lose consciousness stand the best chance of recovery Some patients live only for 4 to 7 days losing ground each day possibly because of a slow continuance of the bleeding It was formerly taught that when a hemorrhage had ruptured into the ventricular system deep coma was invariable Although this is a useful rule of thumb for contrasting brain hemorrhage with ruptured aneurysm where consciousness is more frequently preserved with grossly bloody cerebrospinal fluid there are many exceptions in which the patient is sufficiently alert to respond clearly to questions and commands

In cerebellar hemorrhage vertigo vomiting and ataxia appear first soon followed by coma if the outcome is to be fatal When the hemorrhage is in the pons consciousness is lost rather promptly and death usually occurs within a few hours But in each of these sites the hemorrhage may be arrested and the patient may recover A small cerebellar hemorrhage in particular can present a knotty clinical problem with few or no localizing signs other than a severe disequilibrium which precludes walking or even sitting up for several weeks Persistent dizziness and headache may be associated

Other findings help in the diagnosis of hypertensive brain hemorrhage Vomiting at the onset is the rule A severe headache is often but by no means always present if the patient s mental state permits the appreciation of discomfort Mild to moderate nuchal rigidity will be present but as coma deepens the neck becomes supple again Coma stupor and drowsiness are likely to be much more in evidence in hemorrhage than in cases of infarction In general the existence of a massive hemiplegia in the presence of a relatively well preserved sensorium and alertness speaks against hemorrhage and in favor of infarction

Many of the unlocalized neurologic manifestations described under cerebral thrombosis are also encountered in intracerebral hemorrhage including coma stupor drowsiness confusion delirium Cheyne Stokes respiration grasping and sucking reflexes incontinence of bowel and bladder and unilateral and bilateral extensor rigidity The fundi

often show hypertensive changes in the arteries and occasionally fresh preretinal hemorrhages occur although the latter are much more common in ruptured aneurysm or angioma Grade 4 hyper tension (malignant) with papilledema need by no means be present for cerebral hemorrhage to occur

There is no sex or age predilection except that intracerebral hemorrhage rarely occurs under the age of twenty Hypertension is usually of the "essential type but other causes must always be considered—renal disease pheochromocytoma ACTH overdosage injection of excessive amounts of epinephrine and rarely violent exertion or an intense emotional experience Cardiomegaly is usually present

Although the proper interpretation of this array of clinical data allows the correct diagnosis to be established in most cases the examination of the cerebrospinal fluid for blood is the most important aid in the detection of intracranial bleeding

Laboratory Findings Any urinary abnormalities will for the most part reflect coexisting renal disease although transient glycosuria has been re*ported to result specifically from intracranial hem*orrhage The white blood cell count often rises to 15 000 to 20 000 a higher figure than in thrombosis The sedimentation rate is elevated In cases of massive hemorrhage the cerebrospinal fluid is under increased pressure and grossly bloody although usually not so bloody as in ruptured saccular aneurysm (red cell count of 5 000 to 30 000 per cubic millimeter) In smaller hemorrhages into central structures the cerebrospinal fluid usually contains a lesser amount of blood and in occasional cases of intracerebral hemorrhage particularly in those of the "slit" type between cortex and white matter it remains free of blood and clear of xanthochromia despite repeated taps In these latter cases slight xanthochromia may appear after a few days to a week At times the spinal fluid may contain only some 400 red cells and it is then difficult to decide if this reflects intracranial bleeding or represents a traumatic tap These details are mentioned because they are of importance in the essential task of making an accurate diagnosis of the type of stroke prior to the use of therapeutic measures such as anticoagulant drugs surgical exploration hypothermia etc *A traumatic bloody spinal tap* greatly complicates the diagnostic problem and must be avoided In a bloody tap the pressure is normal or low the fluid that first flows from the needle is more bloody than that which comes later the fluid often clots in the test tube and xanthochromia is either absent or at most present only in proportion to the amount of serum bilirubin admixed with the fluid The bloody fluid due to cerebral hemorrhage is usually under increased pressure there is an even admixture of blood in all samples the cerebrospinal fluid will not clot and if more than a few hours have elapsed since the hemorrhage a definite xanthochromia will be present in the supernatant fluid after centrifugation which should always be carried out if there is any question of the reliability of the tap However the presence of xanthochromia after centrifugation may be due to the bilirubin contained in the blood spilled by a traumatic tap and therefore is not an infallible index of subarachnoid or brain hemorrhage The white blood cells of the cerebrospinal fluid are accounted for by the amount of hemorrhage and their ratio to red cells is usually the same in the circulating blood After hemolysis of red blood cells the white cell count in the cerebrospinal fluid may be disproportionately increased

Lumbar puncture is not completely innocuous since temporal lobe or cerebellar herniation may be aggravated in cases of massive supratentorial hemorrhage or softening and in cerebellar hemorrhage Despite this danger the procedure is necessary if specific therapeutic measures are contemplated or if any doubt exists as to the diagnosis of cerebro*vascular disease X ray of the skull early in the* stroke may show a shift of the calcified pineal gland to the side of the cranium opposite the lesion a change not seen in most infarcts The electroencephalogram does not show a typical or diagnostic pattern but high voltage slow waves are the commonest finding with hemorrhages in the cerebral hemisphere X ray of the chest will often show cardiomegaly and after coma has persisted for a time there may be pulmonary congestion and edema possibly attributable to neurogenic influences

Course and Prognosis The immediate prognosis is grave some 75 per cent of cases dying in 1 to 10 days Either the hemorrhage ruptures under pressure into the ventricular system or temporal lobe herniation and midbrain compression occur Sometimes the hemorrhage appears to seep gradually into vital centers Gastric erosion and gastrointestinal hemorrhage of neurogenic origin may occur at any time within the first week or two When the hemorrhage is smaller survival is possible and the restitution of motor function speech etc can be excellent since in contrast to infarction the hemorrhage pushes brain tissue aside instead of destroying it Function may be slow to return because extravasated blood is slow to be resorbed or removed from the tissues Since rebleeding from the same site is unlikely *the patient may live for* many years In some instances of medium sized cerebral hemorrhages the patient survives and his condition gradually stabilizes but definite papilledema appears after several days of increased intracranial pressure

Treatment *The general medical management of the comatose apoplectic patient is the same as that outlined under thrombosis* Measures to stem the hemorrhage and restore the integrity of damaged tissue have been relatively ineffective up to the present *Surgical removal of the clot* in the acute stage either by aspiration or evacuation has seldom proved successful In the smaller hemorrhages that reach a subacute stage papilledema may appear and has in many instances dictated a surgical evacuation of the hemorrhage when the patient s condition stabilized Under these circumstances the operative procedure has been more successful although the prognosis is probably little improved by surgery Attempts to halt the hemorrhage by lowering the systemic blood pressure through the use of autonomic blocking agents have not been effective and in many instances the inadvertent occurrence of disastrously low levels of blood pressure has complicated the illness Recently artificial hypothermia has given promise of increasing the survival rate but there are insufficient data to permit appraisal of this difficult procedure

The *only preventive measure* is to lower the blood pressure in cases of essential hypertension by every possible means If ACTH or one of the adrenal steroids is being given toxicity must be watched for When hypotension threatens during surgical procedures injections of excessive amounts of epinephrine or ephedrine must be avoided

RUPTURED SACCULAR ANEURYSM

This is the fourth most frequent of the cerebrovascular disorders and presents one of the most disputed therapeutic problems of the day Saccular aneurysms take the form of small thin walled blisters protruding from the arteries of the circle of Willis or the major branches arising therefrom These saccules or berries as they have been called are located for the most part at bifurcations and branchings and are presumed to be the result of developmental defects in the media and elastica at these sites A small number of aneurysms have been attributed to incomplete involution of embryonic vessels Owing to the local weakness the intima bulges outward covered by adventitia the sac gradually enlarges until finally dissolution of the wall and rupture occur These saccular aneurysms vary in size from tiny nubbins 2 mm in diameter up to spherical masses 2 or 3 cm in diameter an average diameter is 8 to 10 mm Aneurysms vary greatly in form some being round and connected to the parent artery by a narrower stalk others are broad based without a stalk and still others are narrow cylinders The dome of the aneurysm may present one or more secondary sacculations In routine autopsies the incidence of ruptured aneurysms is 1 8 per cent of unruptured aneurysms 2 0 per cent

Saccular aneurysms are rare in childhood even at routine post mortem examination and increase in frequency to reach their highest plateau of incidence in the age period of thirty five to sixty five years Therefore they are not congenitally formed anomalies but develop over the years on the basis of a developmental arterial defect There is an increased incidence of congenital polycystic disease of the kidney and of coarctation of the aorta in association with saccular aneurysm Hypertension is more frequently present than in the average population but aneurysms occur in persons with perfectly normal blood pressure Atherosclerosis although present in the walls of about 50 per cent of aneurysms probably plays no part in their formation or enlargement

Eighty five to ninety per cent of saccular aneurysms lie on the anterior part of the circle of Willis The four commonest sites are (1) in relation to the anterior communicating artery (2) at the origin of the posterior communicating artery from the stem of the internal carotid (3) at the first major bifurcation of the middle cerebral artery and (4) at the bifurcation of the internal carotid into middle and anterior cerebral arteries (see Fig 198) Other sites include the internal carotid in the cavernous sinus at the origin of the ophthalmic artery at the junction of the posterior communicating artery with the posterior cerebral at the bifurcation of the basilar artery and at the origins of the three cerebellar arteries In 8 per cent of cases there is more than one aneurysm and they can involve one or both sides of the cerebral circulation[5]

The Clinical Picture Prior to rupture saccular aneurysms are usually asymptomatic and rarely cause even headache Occasionally large aneurysms immediately distal to the cavernous sinus may compress the optic nerves or chiasm the third nerve hypothalamus or pituitary gland In the posterior fossa one or more of the cranial nerves may be compressed as they leave the brain stem

When rupture occurs blood under high pressure *is discharged into the subarachnoid* space (the circle of Willis lies in the subarachnoid space) and

[5] Several types of aneurysm other than saccular occur e g mycotic fusiform diffuse and globular The last three are named for their predominant morphologic aspects and consist of enlargement or dilatation of the entire circumference of the involved vessels usually the internal carotid ertebral, or basilar arteries Frequently showing atherosclerotic *deposition in their walls* they are often referred to as arteriosclerotic, but most likely they are developmental in nature They rarely rupture but instead press on neighboring structures or become occluded by thrombosis

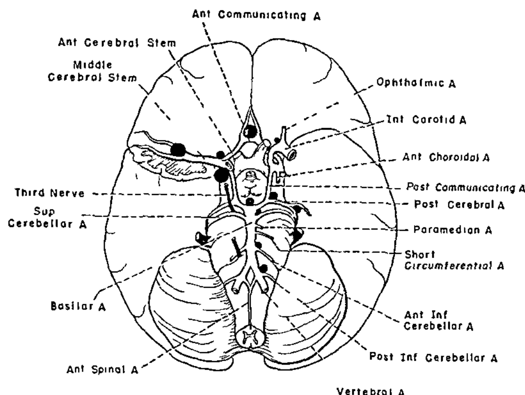


FIG 198 Diagram of the circle of Willis to show the principal sites of saccular aneurysm Approximately 90 per cent of aneurysms are on the anterior half of the circle

the resulting clinical events follow one of three courses (1) the patient may be stricken with an excruciating generalized headache and fall unconscious almost immediately (2) headache may develop as in (1) but the patient remains relatively lucid (3) consciousness may be lost quickly without any preceding complaint Convulsive seizures occur at the onset or during the first week following the hemorrhage in about 10 per cent of patients If the hemorrhage is massive a fatal issue may ensue in a matter of minutes hours or a day or two deep coma persisting in association with labored respiration attacks of extensor rigidity and finally respiratory arrest and circulatory collapse In these rapidly fatal cases the blood has often dissected intracerebrally and may have reached the ventricular system Death occasionally occurs within 5 to 10 min and ruptured aneurysm must be considered in the differential diagnosis of sudden death

In milder cases consciousness may be regained within a few minutes but a residuum of confusion and amnesia persists for a day or two thereafter accompanied by an excruciating headache and stiff neck However it is not uncommon for drowsiness and confusion to last 7 to 10 days or longer If the hemorrhage is confined to the subarachnoid space there are few or no lateralizing neurologic signs

In most patients there are no warning symptoms whatsoever in some however minor leakage from the aneurysm sometimes precedes devastating rupture by a few days or weeks headache being the chief sign of such an event Aneurysmal rupture usually occurs while the patient is active rather than during sleep and sexual intercourse or other exertion has preceded this event in many instances

Although gross lateralizing signs in the form of hemiplegia hemiparesis or aphasia are absent in the majority of cases they are nonetheless frequently encountered They may result from an intracerebral collection of blood due to the rupture of the aneurysm partly into brain tissue as well as into the subarachnoid space (subarachnoid cerebral hemorrhage) in which case the patient often remains comatose or stuporous When the hemorrhage burrows further and ruptures into the ventricular system under high pressure deep coma and death result (subarachnoid cerebroventricular hemorrhage) Often the neurologic deficit clears up in a matter of days The pathogenesis of these milder more transient focal signs which are not attributable to intracerebral bleeding is not clear vasospasm produced by the presence of subarachnoid blood has without good evidence been invoked as the cause Ischemic necrosis of tissue in the territory of the vessel bearing the aneurysm usually without thrombosis may be found post mortem

Although in most patients the neurologic manifestations do not point to the exact site of the aneurysm in many instances hints as to localiza

tion are provided For example (1) third nerve palsy (ptosis diplopia mydriasis and oculomotor paralysis) usually indicates an aneurysm at the junction of the posterior communicating artery and the internal carotid stem The third nerve lies immediately lateral to this point (2) Transient paresis of one or both of the lower limbs at the onset of the hemorrhage is suggestive of an anterior communicating aneurysm which has interfered with the circulation in the anterior cerebral arteries causing ischemia of the motor areas for the lower extremities (3) Hemiparesis or aphasia points to an aneurysm at the bifurcation of the middle cerebral artery which has critically reduced the circulation in the middle cerebral system (4) Unilateral blindness or amblyopia indicates an aneurysm which lies anteromedially in the circle of Willis (at the origin of the ophthalmic artery at the bifurcation of the internal carotid artery or a large aneurysm of the anterior communicating region) (5) A curious state of retained consciousness with akinetic mutism abulia or adynamia favors an aneurysm of the anterior communicating artery which has caused ischemia of or hemorrhage into one or both of the frontal lobes and the corpus callosum The side on which the aneurysm lies may be indicated by a unilateral preponderance of headache or preretinal hemorrhages by the occurrence of monocular pain or by the lateralization of an intracranial sound at the time of rupture of the aneurysm Sixth nerve palsy unilateral or bilateral results from the presence of subarachnoid blood and raised intracranial pressure and is seldom of localizing value Other neurologic signs which have relatively little localizing value include sucking and grasping reflexes choreoathetosis and extensor rigidity

In summary the clinical sequence of sudden and violent headache collapse brief unconsciousness and confusion combined with an absence of prodromal symptoms or a paucity of lateralizing signs is diagnostic of a ruptured saccular aneurysm (or angioma)

Other clinical data are of assistance in reaching a correct diagnosis A fever with the temperature rising to 102 F is common in the first week Nuchal rigidity is usually present Examination of the fundi not infrequently reveals smooth surfaced sharply outlined collections of blood which cover the retinal vessels—the so-called "preretinal or subhyaloid hemorrhages These are usually a sign of ruptured aneurysm or angioma Bilateral Babinski signs are found in the early days following rupture especially if there is impairment of consciousness The patient may appear to be normally alert yet impairment of memory and confabulation may be present on more careful testing A faint intracranial bruit the mechanism of which is not clear may rarely be heard and may indicate an angioma

Spontaneous intracranial bleeding with normal blood pressure should always suggest ruptured aneurysm ruptured angioma or hemorrhage into a cerebral tumor The escaping blood occasionally enters the subdural space and produces a subdural hematoma evacuation of which may be lifesaving Aneurysmal rupture may complicate pregnancy but pregnancy is not associated with an increased incidence of aneurysmal rupture

Carotid and vertebral angiography using Diodrast or Hypaque will demonstrate the aneurysm in some 70 per cent of patients in which aneurysm seemed to be the correct diagnosis on clinical grounds i e in cases of so-called "spontaneous subarachnoid hemorrhage X rays of the skull are usually negative though in a few patients one or both of the anterior clinoid processes has been eroded by the pressure of an adjacent aneurysm or calcification has occurred in the region of a previous hemorrhage A calcified pineal gland may be shifted because of an intracerebral or subdural clot

The electroencephalogram is of little help in lateralizing the lesion unless a gross neurologic deficit is present in which case the lateralization is probably already evident clinically The abnormality usually consists of slow waves

Laboratory Findings Urinary examination may reveal transient glycosuria and albuminuria and rarely diabetes insipidus Any other urinary abnormalities are due to concomitant renal disease A leukocytosis of 15 000 to 18 000 is common The cerebrospinal fluid is usually extremely bloody with red cell counts reaching to 1 000 000 per cubic millimeter or higher It is unlikely that an aneurysm can rupture entirely into brain tissue without some leakage of blood into the subarachnoid fluid and therefore the diagnosis of ruptured saccular aneurysm must never be made unless blood is present in the spinal fluid (Only expanding saccular aneurysms which compress the optic nerves and chiasm or cranial nerves and intracavernous aneurysms produce symptoms without hemorrhage) Usually deep xanthochromia is found after centrifugation The cerebrospinal fluid is under greatly increased pressure as high as 1 000 mm of fluid (see p 294 regarding traumatic tap) The white blood cells in the spinal fluid are usually present in the same proportion to red blood cells as pertains in the circulating blood but within 48 hr a brisk leukocytosis appears reaching to 2 000 to 3 000 per cubic millimeter in some patients

Course and Prognosis It is estimated by Walton from studies based for the most part on clinically diagnosed cases that approximately 30 per cent of patients die as the result of the first hemorrhage—15 per cent in the first 24 hr 15 per cent in the following 13 days In many of these cases sub

arachnoid cerebral or subarachnoid cerebroventricular hemorrhage has occurred Unlike cases of primary intracerebral hemorrhage recurrence of bleeding is common in saccular aneurysms and rerupture is responsible for death in another 20 per cent of cases in the 6 weeks following the initial ictus with a decreasing incidence of fatal hemorrhages thereafter Recurrence is most common in the second week The threat of recurrence therefore colors all prognostications and unfortunately there appears to be no reliable way of determining in which cases rebleeding will occur If recurrence does not mar recovery the restoration of normal function will depend on the severity of the neurologic change In cases of mild to moderate severity without lateralizing signs full recovery is the rule However one third of the survivors are completely or significantly disabled by paralysis epilepsy mental deterioration or headache Chronic cerebral seizures are an aftermath in about 5 per cent of cases A few patients develop a chronic obstructive or communicating hydrocephalus with persistent headache and confusion or stupor relieved by ventricular drainage Each successive recurrence of bleeding carries with it the same grave prognosis as the initial one and very few patients survive three hemorrhages If they do a disabling neurologic deficit usually remains A succession of subarachnoid hemorrhages five or more always suggests an angioma The cause of the intermittency of bleeding is not understood Patients with the typical clinical picture of spontaneous subarachnoid hemorrhage but in whom the angiogram shows no aneurysm or angioma have a much better prognosis than those in whom the lesion is demonstrated

Treatment General medical management in the acute stage is similar to that described under cerebral thrombosis (p 1583) Any specific measures are based on the assumption that decreasing the arterial blood pressure is the most reasonable way of arresting bleeding and preventing further bleeding Absolute bed rest for 4 to 8 weeks is prescribed with the head of the bed raised some 15 to 20 Straining during bowel movement is forbidden and laxatives or gentle enemas are administered Coughing and all forms of exertion are carefully avoided The patient is fed The duration of the period of bed rest is empirical and not founded on any observations on the formation of scar tissue around aneurysms Sedatives (barbiturates) and analgesics (opiates acetylsalicylic acid) are important in aiding relaxation The use of hypotensive agents has been widely suggested no proof of their efficacy has been presented In the presence of severe hypertension hexamethonium orally or by injection may be cautiously used to lower the blood pressure to 160/100 great care being exercised not to precipitate cerebral infarction Hexamethonium and chlorpromazine are usually not effective in lowering the blood pressure of normotensives confined to bed Chlorpromazine intramuscularly is used to control nausea and vomiting Dilantin or phenobarbital is prescribed routinely to prevent cerebral seizures

The place of repeated drainage of the cerebrospinal fluid by lumbar puncture is still uncertain although several workers have found it makes no difference in the outcome of the illness At present one lumbar puncture is usually carried out for diagnostic purposes and thereafter it is performed only for the relief of intractable headache to detect recurrence of bleeding or to measure the intracranial pressure prior to arteriography or surgery

In maintaining fluid balance intravenous fluids should be used sparingly and in the proper electrolyte combination (a mixture of equal parts of 5 per cent glucose in water and normal saline solution or balanced electrolytes) in order to minimize the danger of aggravating brain swelling Any abnormality of concentration of electrolytes in the blood must be corrected Diabetes insipidus is treated with pitressin Disorders of blood coagulation should be amended Vitamins C and K have been recommended but there is no evidence that they are beneficial The use of body hypothermia for 2 to 5 days in the stage of acute hemorrhage has recently been introduced but cannot yet be evaluated

After resting in bed for 6 weeks the patient is gradually allowed to resume activity and may return to work in 4 months Usually heavy laboring work is forbidden although this advice is not based on recorded experience

Surgical Therapy Surgical treatment has been for the most part directed to the prevention of the recurrence of hemorrhage The procedures are either *extracranial* (ligation of the common carotid in the neck) or *intracranial* (resection of the aneurysm ligation of the neck of the aneurysm wrapping or tamponade of the aneurysmal sac by muscle fascia or arterial graft trapping the aneurysm ligation of the main vessel proximal to aneurysm) Occasionally extracranial and intracranial procedures are combined Because of the high operative mortality if surgery is undertaken early operation has usually been delayed until the patient s condition has stabilized following the first hemorrhage During the waiting period however about 25 per cent of patients will suffer a further hemorrhage and it is in an effort to reach these patients before rebleeding occurs that neurosurgeons are now attempting to operate much earlier than formerly using hypothermic and hypotensive anesthesia Before surgery is undertaken the site size

and form of the aneurysm must be determined by bilateral carotid angiography At the same time the pattern of the anterior half of the circle of Willis is noted as it may influence the choice of operative procedure

OTHER CAUSES OF INTRACRANIAL HEMORRHAGE

1 *Angioma* An angioma or hemangioma consists of a tangle of vessels of varying size forming an abnormal communication between the arterial and venous systems It is a developmental abnormality and not a neoplasm but the constituent vessels enlarge with growth and the passage of time Angiomas vary in size from small blemishes a few millimeters in diameter lying in the cortex to huge masses of tortuous channels comprising an arteriovenous shunt of sufficient magnitude to raise the cardiac output Hypertrophic dilated arterial "feeders" approach the main lesion disappear below the cortex, and break up into a network of thin walled blood vessels which connect directly with draining veins The latter often form huge dilated pulsating channels carrying away arterial blood Angiomas occur in all parts of the brain brain stem and spinal cord but the larger ones are more frequently found in the middle and anterior cerebral territories commonly forming a wedge-shaped lesion extending from the cortex to the ventricular lining The blood vessels forming the tangle interposed between arteries and veins are usually abnormally thin and do not have the normal structure of arteries or veins

This condition predominates in males over females about 2 1 Although the lesion is present from birth, the onset of complaints is most common between the ages of ten and thirty but occasionally is delayed as late as the fifties The chief clinical features are epileptic seizures and cerebral subarachnoid hemorrhage In 50 per cent the first manifestation is a fit in 20 per cent an intracerebral hemorrhage with hemiplegia and in 20 per cent a typical subarachnoid hemorrhage The seizures are usually focal motor in type and may be followed by a temporary postictal paralysis When hemorrhage occurs blood may enter the subarachnoid space almost exclusively producing a picture identical with that of ruptured saccular aneurysm or since the angioma lies within cerebral tissue the bleeding may be partly intracerebral resulting in a deficit such as hemiparesis Nondescript headache is a frequent complaint and occasionally typical migraine is associated but whether it is the result of the angioma or a coincidence is not certain A systolic intracranial bruit heard best over the eye balls is in young adults almost pathognomonic of angioma The eye grounds may reveal a retinal vascular abnormality The blood pressure may be raised or normal—and it is axiomatic that the occurrence of intracranial bleeding with normal blood pressure should lead to the suspicion of an angioma ruptured saccular aneurysm or hemorrhage into a tumor Preretinal hemorrhages may be found after hemorrhage has occurred X ray of the skull occasionally shows crescentic linear calcification in the vicinity of the larger angiomas Pneumoencephalography may show the picture of an expanding lesion combined with cerebral atrophy a combination typical of angioma. Arteriography is necessary to establish the diagnosis with certainty

Most angiomas bleed sooner or later The first hemorrhage may be fatal but most often bleeding stops for some reason and the patient survives Recurrence of the hemorrhage with a fatal outcome is a constant danger In recent years it has been the practice of neurosurgeons to perform a block dissection and removal of suitably located and localized angiomas

2 *Trauma* Although intracranial bleeding due to head trauma does not rightfully fall within the scope of the stroke problem it must be mentioned here because of the great frequency with which it enters into the differential diagnosis especially in stroke cases in which the history is inadequate or in which the patient falls and injures himself at the onset of the stroke *Acute extradural* and *acute subdural hemorrhage* must always be considered in the patient who under unknown circumstances has abruptly developed a neurologic deficit such as hemiparesis or confusion whether the spinal fluid is bloody or not In *chronic subdural hemorrhage* which can occur without known trauma the indefinite picture of drowsiness confusion and mild hemiparesis may be erroneously attributed to a stroke especially in the elderly person These three conditions must be constantly kept in mind since failure to make the correct diagnosis deprives the patient of surgical intervention which is usually most effective There should be no hesitation in placing diagnostic burr holes a relatively minor procedure in all patients in whom subdural hemorrhage cannot be excluded on clinical grounds *Cerebral contusion* and *laceration* may be a cause of subarachnoid hemorrhage and if the patient has fallen and struck his head at the time of the onset of the stroke it may be difficult or impossible to decide if the red blood cells in the cerebrospinal fluid are due to a cerebrovascular stroke or to cerebral contusion Trauma may also be the cause of *acute or delayed intracerebral hemorrhage acute intracerebellar hemorrhage acute brain swelling* and on rare occasions extensive *focal infarction* of undetermined pathogenesis

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INFLAMMATORY DISEASES OF BRAIN ARTERIES

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Meningovascular syphilis formerly one of the most frequent causes of occlusive vascular disease in patients of all ages has become a rarity since the introduction of penicillin therapy Neurosyphilis is basically a chronic treponemal cerebrospinal meningitis and as in all forms of chronic meningitis the subarachnoid vessels become involved in the inflammatory process This is the reason for calling syphilitic vascular disease of the brain *meningovascular* If the arteritis is active and symptoms of vascular occlusion are of recent origin there are almost invariably signs of meningitis as evidenced by the elevated cerebrospinal fluid protein and cells and its syphilitic nature is revealed by the positive Wassermann reaction Syphilis must still be considered as a diagnostic possibility in all patients who suffer a brain infarct particularly at an early age In the experience of the authors however the usual error is to assume that a stroke is syphilitic when in fact some other arterial disease is the cause If the cerebrospinal fluid is normal or inactive" meaning that it has normal cell and protein values a stroke will nearly always prove to be nonsyphilitic even when the blood Wassermann reaction is positive Formerly syphilis was erroneously assumed to be the cause of cerebral aneurysms or rupture of vessels with intracerebral or meningeal hemorrhage but now the diagnosis is rarely entertained

Tuberculous meningitis fungous meningitis and the subacute forms of bacterial meningitis (influenzal bacillus staphylococcus pneumococcus) may also be accompanied by vascular disorders of occlusive type in either the cerebral arteries or veins Occasionally in tuberculous meningitis a stroke may be the first clinical sign of meningitis more often it develops after the meningeal symptoms are well established The diagnosis of these meningeal diseases is relatively simple for the cerebrospinal fluid contains the essential clues A treatment which suppresses the meningitis also controls the arteritis *Septic embolism* may be a source of arteritis and sometimes of mycotic aneurysm formation The latter may rupture and cause either cerebral or subarachnoid hemorrhage but more often the clinical manifestations are those of arterial occlusion

Typhus schistosomiasis mansoni mucormycosis malaria and *trichinosis* are rare types of infective inflammatory diseases of the arteries and unlike the above are not secondary to meningeal inflammation The cerebrospinal fluid may be normal or abnormal In typhus and other rickettsial diseases capillary and arteriolar changes and perivascular inflammatory cells are found in the brain and presumably they underlie the convulsions acute psychoses and coma which reflect the central nervous system involvement The internal carotid artery may be occluded in diabetic patients during orbital and cavernous sinus infections with mucormycosis In *trichinosis* the sudden onset of convulsions aphasia hemiplegia and coma may either accompany or more often follow the systemic and muscular symptoms The cause of the cerebral symptoms has not been established Parasites have been found in the brain and in one case known to the authors the cerebral lesions were produced by bland emboli arising in the heart and related to a severe myocarditis Malaria of the malignant or falciparum variety is frequently attended by a clinical state known as "cerebral malaria in which convulsions and coma and sometimes focal symptoms appear to be due to blockage of capillaries and precapillaries by masses of parasitized red blood corpuscles

The *arteritides of obscure origin* include disseminated lupus erythematosus polyarteritis nodosa rheumatic arteritis granulomatous arteritis giant cell arteritis and cranial (temporal) arteritis In systemic lupus erythematosus delirium confusional states convulsions hemiplegia and aphasia and brain stem or cerebellar syndromes may be traced to occlusion of small arteries either by thrombosis or in those cases with Libman Sacks endocarditis by embolism Intracerebral hemorrhage and hypertensive encephalopathy often terminate the illness if renal hypertension has developed

Rheumatic arteritis is still a highly debatable subject Pathologic studies have not provided convincing evidence of a primary arteritis In many of the reported cases infarction which has been the usual parenchymal brain lesion was due to embolism from a rheumatic endocarditis However the close relationship of lupus erythematosus in which there is an arterial lesion and rheumatic fever offers a plausible basis of a primary inflammation of cerebral vessels

Polyarteritis nodosa frequently involves the small blood vessels in the peripheral nerves giving rise to a clinical picture of a multiple asymmetric or symmetric sensorimotor *polyneuropathy* and cerebral vessels usually escape If hypertension becomes severe as it often does brain hemorrhage or hypertensive encephalopathy may occur More recently a granulomatous form of polyarteritis nodosa has been delineated in which the neurologic syndrome has been more encephalitic than vascular with headache ataxia confusion convulsions hemiparesis etc In these latter cases a moderate increase in white blood cells and total protein of the cerebrospinal fluid provides further evidence

3 Several *hemorrhagic hematologic disorders* may at some stage be complicated by hemorrhage into the brain The most frequent of these are leukemia aplastic anemia and thrombopenic purpura As a rule this complication signals a fatal issue Any part of the brain may be involved and not infrequently the lesions are multiple Usually there is already evidence of abnormal bleeding elsewhere (skin mucous membranes kidney) by the time cerebral hemorrhage occurs Intracranial bleeding is a rare complication of anticoagulant therapy

4 On infrequent occasions bleeding within an area of *hemorrhagic* infarction reaches major proportions forming an intracerebral hematoma and the cerebrospinal fluid becomes bloody

5 Brain stem hemorrhages secondary to temporal lobe herniation are extremely common but never present as a cerebrovascular stroke

6 *Hemorrhage into primary and secondary brain tumors* is not rare and when it is the first manifestation of the neoplasm the correct diagnosis may be extremely obscure Chorionepithelioma melanotic carcinoma renal cell carcinoma bronchogenic carcinoma pituitary adenoma glioblastoma multiforme and medulloblastoma may present themselves in this way Careful inquiry will usually disclose the fact that signs of a neurologic disorder compatible with intracranial tumor growth have preceded the onset of hemorrhage Examination directly and by x ray may reveal evidence of intracranial tumor or of secondary tumor deposits in other organs A chest film will frequently reveal evidence of metastatic or primary neoplasm and should be performed in all cases of obscure intracerebral hemorrhage

7 *Septic embolism* may lead to massive fatal intracranial bleeding via the production of a *mycotic aneurysm* Any part of the circulatory tree may be involved but usually the aneurysm lies at a branching or forking of a small vessel (about 0 5 mm in diameter) within the subarachnoid space

8 *Hypertensive encephalopathy* may in its most advanced stage result in intracerebral hemorrhages which can vary in size from the massive type down to petechiae

9 *Idiopathic brain purpura* or hemorrhagic encephalitis consists of multiple petechial hemorrhages scattered throughout the white matter of the brain The picture is that of a diffuse cerebral disease There is never blood in the spinal fluid and the condition should never be confused with a typical stroke

10 *Inflammatory* disease of arteries and veins—more specifically polyarteritis nodosa and lupus erythematosus—may give rise to medium sized hemorrhages especially if renal hypertension develops However because of their relatively small size they do not clinically resemble primary intracerebral hemorrhage

11 *Hemorrhages of undetermined origin* Although this is the final category it is nonetheless important since both clinically and pathologically hemorrhages are found in which the blood pressure is normal and neither an aneurysm nor angioma can be demonstrated In some post mortem cases a careful microscopic search discloses a small angioma in the cerebral tissue at one side of the hemorrhage and on this basis it is suspected that in other cases too an overlooked angioma may have been the cause of the extravasation of blood Primary intraventricular hemorrhage a rare event is at times due to angioma or neoplasm of the choroid plexus which may not have been seen by the prosector

HYPERTENSIVE ENCEPHALOPATHY

This term refers to an acute syndrome in which severe hypertension is associated with headache nausea vomiting convulsions confusion stupor and coma Focal or lateralizing neurologic signs either transitory or lasting are rare and always suggest some other form of vascular disease (hemorrhage embolism atherosclerotic thrombosis) By the time the neurologic manifestations appear the hypertension has usually reached the malignant stage with retinal hemorrhages exudates papilledema (formerly called *uremic retinopathy* now known as *hypertensive retinopathy* grade IV) and evidence of renal and cardiac disease The cerebrospinal fluid pressure and the protein values are both elevated in many but not all of the cases the latter sometimes over 100 mg per cent The hypertension may be essential or due to chronic renal disease acute glomerulonephritis eclampsia pheochromocytoma Cushing s syndrome or ACTH toxicity Lowering of the blood pressure with hypotensive drugs may reverse the picture in a few days or sooner If the hypertension cannot be controlled the patient usually dies within a few days weeks or months Neuropathologic examination may reveal a rather normal looking brain but usually one or more gross changes can be demonstrated including cerebral swelling large and small hemorrhages and petechial hemorrhages Frequent microscopic findings are clusters of glial cells necrosis of arterioles and minute cerebral infarcts

The term *hypertensive encephalopathy* should be reserved for the above syndrome and not used to refer to chronic recurrent headaches dizziness epileptic seizures recurrent transient ischemic attacks or small strokes which often occur in association with high blood pressure For further discussion see p 1363

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that the illness is not an ordinary type of vascular disease

Cranial arteritis (temporal arteritis) is an uncommon affliction of elderly persons in which the branches of the external carotid arteries particularly the temporal ones are the seat of a subacute granulomatous inflammation with an exudate of lymphocytes monocytes neutrophilic leukocytes and giant cells Usually the most severely affected parts of the artery become thrombosed This aspect of the disease is distressingly painful The inflammatory nature of the illness is betrayed by fever slight leukocytosis increased sedimentation rate and sometimes anemia Occlusion of the ophthalmic arteries may result in blindness in one or both eyes in over 50 per cent of patients and occasionally an ophthalmoplegia due to involvement of ocular nerves occurs Although strokes have been observed in these patients significant inflammatory involvement of intracranial arteries has rarely been demonstrated An arteritis of the aorta and its major branches including carotid subclavian coronary and femoral arteries has been found in a few fatal cases in which a post mortem examination was made Meticorten and ACTH bring striking subjective relief but whether or not they prevent blindness has not been clearly decided See p 1708 for further discussion

A closely related disease called *giant cell arteritis* may affect younger people in it all the branches of the aorta including the common carotid arteries may become occluded This disease was described long ago in Japan (Takayasu) and in Norway (Harbitz) The vascular pathology is not well defined but chronic inflammation with destruction of all coats of the vessel infiltrates of lymphocytes plasma cells and mononuclear leukocytes the presence of giant cells and thrombosis comprise the lesion The cause of the disease is unknown There is no information concerning therapy See Chap 229 and p 1570

Thromboangiitis obliterans (Winiwarter Buerger disease) of cerebral vessels is not included in the classification Despite the large amount of literature on the subject the pathology is so dubious that it does not merit further exposition All the patients that the authors have studied proved to have had either atherosclerosis of the carotid or cerebral arteries with stasis thrombosis" of more distal cerebral branches Buerger s disease of the legs has an equally uncertain status

THE DIAGNOSIS OF CEREBROVASCULAR DISEASE

There are two separate aspects to the problem of differential diagnosis (1) vascular disease must be distinguished from other neurologic illnesses (2) the different kinds of vascular diseases must be separated from one another In the following pages many of the important points discussed in the body of the chapter will be recapitulated

1 *Differentiation of vascular disease from other neurologic illnesses* It has already been stated that the diagnosis of a vascular lesion rests solely on the recognition of the cerebrovascular stroke and that without evidence of this the diagnosis must always be in doubt Three criteria have already been emphasized as having practical utility in the identification of the stroke (*a*) the temporal profile of the clinical syndrome (*b*) evidence of focal brain disease and (*c*) the clinical setting The clinical profile can usually be ascertained by a clear history of premonitory phenomena the mode of onset and the evolution of the neurologic disturbance taken in relationship to the medical status at the time of examination If these data are lacking the course may still be determined by extending the period of observation over days or weeks thus resorting to the clinical rule that the physician s best diagnostic tool is the second and third examination An inadequate history is probably the most frequent cause of diagnostic errors

As stated above the neurologic deficit in a cerebrovascular stroke nearly always develops suddenly and in the later part of its course if death does not occur stabilization and some degree of recovery take place There are few neurologic illnesses whose temporal profile mimics that of cerebrovascular disorders Tumor infection inflammation degeneration and nutritional disorders are not likely to manifest themselves precipitously In trauma of course a sudden insult occurs but usually injury is readily recognizable as the cause Multiple sclerosis and other demyelinative diseases often have abrupt episodes of exacerbation but are seldom as sudden in onset as vascular diseases and for the most part they occur in a different age group and clinical setting

Many thrombotic strokes are preceded by transient ischemic episodes which if they are nonconvulsive in nature are almost diagnostic of vascular disease Their differentiation from cerebral seizures attacks of Ménière s syndrome and paralytic migraine was discussed in the description of intermittent cerebral ischemia A stroke developing over a period of several days usually progresses in a stepwise fashion rather than evolving smoothly increments of additional deficit are added serially from time to time A slow gradual downhill course over a period of days or weeks indicates that the lesion is probably not vascular but rather a tumor abscess granuloma or subdural hematoma

The focal neurologic deficit in cerebrovascular disease is usually a hemipl[illegible] of face arm and

leg associated with hemianesthesia or hemihypesthesia homonymous hemianopia aphasia agnosia etc but it is obvious from the above descriptions that there are many other manifestations which must be recognized as the product of vascular disease However many nonvascular neurologic diseases (tumor abscess etc) also produce focal neurologic deficits which are not strikingly different from those resulting from vascular disease and the diagnosis usually cannot rest solely on this aspect of the clinical picture Nonetheless certain combinations of neurologic signs which conform to a neurovascular pattern e g the lateral medullary syndrome are seen almost exclusively in occlusive vascular disease

The presence of blood in the cerebrospinal fluid always points to a cerebrovascular lesion providing that trauma and a bloody tap can be excluded It must be repeated that *headache* is not infrequent as a prodromal manifestation or an actual accompaniment of the development of a thrombotic stroke *Cerebral seizures* almost never the premonitory manifestation of a stroke can occur early in the course of intracranial bleeding but are extremely uncommon early in the course of infarction (the first 2 days) *Brief unconsciousness* (5 to 10 min) is rare in stroke cases being seen only in ruptured aneurysm The presence of certain neurologic disturbances which occur rarely in cerebrovascular disease e g diabetes insipidus bitemporal hemianopia parkinsonism generalized myoclonus and isolated cranial nerve palsies may be of help in ruling out the diagnosis

Finally it is recommended that the diagnosis of cerebrovascular disease always be made on positive data Diagnosis by exclusion is too precarious

A few conditions are so often confused with the cerebrovascular diseases that they merit further consideration When a history of trauma is absent the headache drowsiness and mild hemiparesis accompanying a *subdural hematoma* may all too easily be ascribed to a slight stroke and the patient may fail to receive immediate surgical therapy In classic subdural hematoma the symptoms and signs will usually develop gradually over a period of days or weeks The degree of obtundation and confusion will often be disproportionately great in comparison with the focal neurologic deficit which tends to be indefinite and variable Short of arteriography pneumoencephalography or operation a subdural hematoma may be indicated by finding in the x ray of the skull a fracture line or a shift of the pineal gland The cerebrospinal fluid may be blood tinged or xanthochromic where the type of stroke under suspicion would not be expected to show this The electroencephalogram occasionally is strikingly silent over a subdural hematoma and this may be of help in diagnosis If the patient has fallen and injured his head at the onset of the stroke it may be impossible to rule out a complicating subdural hematoma without performing diagnostic burr holes

The reverse diagnostic error of mistaking a stroke for a subdural hematoma is also often made Here it is helpful to remember that patients with subdural hematoma rarely exhibit a complete hemiplegia a monoplegia a hemianesthesia a homonymous hemianopia or a well-developed aphasia If these focal signs are present and particularly if they developed suddenly the diagnosis of subdural hematoma is far less likely than stroke

A *brain tumor* especially a rapidly growing glioblastoma multiforme which may produce a severe hemiplegia within a week or two is often mistaken for a stroke Secondary carcinoma also may quickly lead to a marked neurologic deficit However in both conditions a detailed history will show that the course was gradual and if the symptoms progressed in saltatory fashion it was usually punctuated by seizures A routine chest film will be of great help in detecting a primary or secondary source of cancer in the lung An increased blood sedimentation rate may suggest that a systemic disease process is at work Rarely a *brain abscess* occurs without any known primary antecedent focus of infection and may not be considered in the diagnosis especially if the patient is elderly

Senile dementia with its progressive loss of memory and enfeeblement of the intellect is often ascribed on insufficient grounds to multiple small strokes possibly in silent areas of the brain If vascular lesions are responsible evidence of them will be divulged by the history (sudden onset episodic development) and by examination (a focal neurologic deficit motor sensory aphasia etc) The commonest cause of mental deterioration in the elderly patient is Alzheimer s disease or related degenerative processes and in the absence of focal neurologic signs it is unwarranted to assign cerebral vascular disease—in particular small strokes in silent areas—as the cause of this syndrome Cerebral arteriosclerosis is another term used too loosely as an explanation for such mental changes the inference being that multiple areas of focal ischemia irreparably damaged the nervous system producing loss of memory but no other focal neurologic signs If cerebral arteriosclerosis (atherosclerosis) is actually responsible there should be evidence of it in the brain (strokes) heart (myocardial infarction angina pectoris) or legs (intermittent claudication)

Chronic cerebral seizures occur as the result of the stroke (*poststroke seizures*) in some 20 per cent of cases When the seizures are infrequent or not properly observed or when they leave behind a temporary increase in the neurologic deficit

(Todd s paralysis) the diagnosis of another stroke may be made in error

Fear anxiety and *depression* in patients who have had one small stroke may lead to additional symptoms such as alterations in the paresthesias headache or disequilibrium which suggest to the patient and his physician that further vascular lesions have occurred or threaten

Miscellaneous conditions which occasionally lead to the suspicion of a stroke are Bell s palsy Stokes Adams attacks diabetic ophthalmoplegia acute ulnar radial or peroneal palsy embolism to a limb and cranial arteritis associated with blindness

Strokes may be wrongly diagnosed as other neurologic illnesses This happens under a variety of circumstances but often it is because of inability to obtain a detailed history with the result that the mode of development of the focal neurologic deficit remains in question Unfortunately some of these patients who are subjected to pneumoencephalography for the diagnosis of these other conditions sometimes develop widespread brain infarction because of the fall in the systemic blood pressure during the procedure In the lateral medullary syndrome *dysphagia* may be the outstanding feature if the syndrome is not kept in mind the patient may be suspected of harboring an esophageal neoplasm and a fruitless surgical investigation may be entered into *Headache* at times occurs as the prodrome of an oncoming thrombotic stroke unless this is appreciated a diagnosis of migraine may be reached The diagnosis of such an illness occurring *for the first* time in a middle aged patient should be made only with great reluctance In the elderly patient *vertiginous attacks* due to vascular disease of the brain stem may be diagnosed as labyrinthine disease or Meniere s syndrome (see Chap 29) Stokes Adams syncopal attacks or paroxysmal tachycardia may be erroneously diagnosed when dizzy spells or brief lapses or intermittent loss of equilibrium are the principal manifestation of cerebrovascular disease A detailed account of the attack will usually serve to circumvent this error A strikingly focal monoplegia of cerebral origin involving only the hand or producing only a foot drop is not infrequently misdiagnosed as a peripheral lesion

The differentiation of vascular disease from other neurologic illnesses in the presence of coma offers special problems If the patient is comatose when first seen and an adequate history is not available cerebrovascular lesions will have to be differentiated from all the other causes of coma described on p 314 In most cases some history will be at hand to assist in the series of diagnostic deductions described below The cerebrovascular causes of coma are as follows hypertensive intracerebral hemorrhage ruptured saccular or mycotic aneurysm ruptured angioma basilar artery embolism or thrombosis acute hypertensive encephalopathy with brain edema extensive infarction including most of one cerebral hemisphere (due to occlusion of a major arterial trunk) bilateral occlusion of the internal carotid arteries bilateral cerebral embolism multiple septic emboli and widespread cerebral ischemia due to systemic hypotension (shock due to gastrointestinal bleeding myocardial infarction ruptured aneurysm Stokes Adams attacks syncope) Nearly all these forms of cerebrovascular coma are accompanied by focal or lateralizing neurologic signs or changes in the cerebrospinal fluid which aid in separating them from toxic and metabolic abnormalities (see Chap 33)

2 *Differentiation of thrombosis embolism and hemorrhage* It is difficult to set up hard and fast rules but usually it is possible to distinguish the three conditions at the bedside

The most important criteria of *atherosclerotic thrombosis* are (1) a history of prodromal transient ischemic attacks (2) an intermittent or stepwise evolution of the neurologic deficit often with recovery or improvement between worsenings rather than a steady progression (3) relative preservation of consciousness unless the upper part of the basilar territory is infarcted (4) clear cerebrospinal fluid (except in meningovascular syphilis intracranial arteritis and occasionally an idiopathic pleocytosis with bland infarction) (5) the occurrence of rapid improvement at times (6) onset during sleep or shortly after arising while eating or during a period of hypotension (7) certain constellations of symptoms and signs e g the lateral medullary syndrome (8) evidence of atherosclerosis elsewhere especially in the coronary and peripheral vessels and aorta (9) the presence of disorders usually associated with atherosclerosis (hypertension diabetes mellitus and xanthomatosis) (10) headache of moderate severity (may be prodromal warning or may accompany stroke) (11) contralateral cranial bruit (may indicate carotid occlusion of thrombotic type) (12) occlusion of the internal carotid artery in the neck whether spontaneous" or posttraumatic (usually of thrombotic origin)

Cerebral embolism is characterized by (1) sudden onset of the clinical picture within a period of a few seconds or minutes (2) the absence of prodromal transient ischemic attacks (rarely one or two transitory episodes occur in embolism) (3) a source of embolus usually in the heart—atrial fibrillation or other arrhythmia myocardial infarction subacute bacterial endocarditis mitral stenosis valvulotomy marantic endocarditis associated with carcinoma (4) evidence of recent embolism in other organs i e spleen kidney extremities gastrointestinal tract or lungs (5) evidence of recent involvement of several regions of the brain

in different cerebrovascular territories (6) clear cerebrospinal fluid except in those cases in which extensive bleeding occurs in an area of hemorrhagic infarction (most often even in hemorrhagic infarction the cerebrospinal fluid is clear or at most *faintly xanthochromic*) (7) rapid improvement (many embolic strokes produce persistent deficits but it is not uncommon for an extensive focal cerebral disorder to reverse itself in minutes or hours) (8) relative preservation of consciousness in the presence of extensive neurologic deficit unless the upper part of the basilar territory is affected or massive brain swelling *has occurred with temporal* lobe tentorial herniation (9) occurrence at an age when atherosclerosis is usually not a factor and in the absence of hypertension arteritis or infection (10) a *headache* of moderate severity which not infrequently accompanies cerebral embolism

Other causes of cerebral infarction The *diagnosis of arteritis* as a cause of infarction is justifiable only in the following circumstances (1) evidence of an arteritis elsewhere (2) in young individuals who manifest neither hypertension nor signs of cardiovascular disease and (3) in individuals with a meningeal infection which could affect the meningeal vessels (syphilis tuberculosis) *Venous thrombosis with infarction* should be especially considered when focal neurologic signs develop after an operation or in the period following parturition in the course of meningeal infection ear or sinus suppuration diseases which result in cachexia and sickle cell disease or polycythemia

In *hypertensive cerebral hemorrhage* the diagnosis rests on (1) history of the gradual development of a deficit over a period of 10 to 15 min or more (sometimes the onset appears to have been *abrupt*) *(2) absence of any prodromal phenomena* (3) presence of hypertension (4) grossly bloody spinal fluid under elevated pressure due to rupture of the hemorrhage into the ventricles (this is not invariable—there are cases in which the hemorrhage does not extend to the ventricular system to reach the cerebrospinal fluid accurate diagnosis *is difficult in these patients*) (5) *deepening coma* and general deterioration of the neurologic condition (in general if there is an extensive paralysis the patient is likely to be deeply or moderately stuporous if not comatose a cerebrovascular stroke which leaves the patient alert and the mind relatively clear proves in nearly all instances to be due to an infarct) (6) *severe headache often but* not invariably present (7) a lateral displacement of the pineal gland (evidence of a hemorrhage rather than of an infarct provided that massive brain swelling can be excluded) (8) the neck being supple or only mildly rigid on forward flexion (9) persistence of the neurologic deficit (an evanescent stroke is never due to a hemorrhage since extravasated blood is removed very slowly from the brain tissues) (10) onset during waking hours rather than in sleep

The *chief clinical features of ruptured saccular aneurysm* are (1) sudden onset of severe headache with or without a transient disturbance of consciousness (in the most severe cases coma persists and the patient dies within a few hours) (2) stiff neck on forward bending Kernig and Brudzinski signs (3) grossly bloody spinal fluid under increased pressure (rupture of a saccular aneurysm without subarachnoid hemorrhage rarely if ever *occurs except in the case of aneurysms within the* cavernous sinus grossly bloody cerebrospinal fluid in the presence of a third nerve palsy indicates a ruptured aneurysm at the origin of the posterior communicating artery from the internal carotid artery) (4) absence of hypertension in many cases (5) onset during exertion sexual intercourse etc (6) usually an absence of prodromal warnings although there may be a history of one or more premonitory leaks associated with transient headache (7) preretinal (subhyaloid) hemorrhages (these suggest ruptured aneurysm or angioma although they can occur in massive intracerebral hemorrhage) (8) a relative absence of focal neurologic signs Saccular aneurysm is likely to produce a diffuse subarachnoid hemorrhage without causing significant damage to the cerebral hemispheres If the cerebrospinal fluid is *bloody and the patient* retains mental clarity or is only mildly confused aneurysm is the diagnosis of choice If the aneurysm bleeds into the brain tissue (subarachnoid-cerebral hemorrhage) or into the ventricular system also (subarachnoid cerebroventricular hemorrhage) focal neurologic signs and coma ensue as in intra*cerebral hemorrhage Cerebral infarction associated* with ruptured aneurysm not an uncommon event is another cause for a focal neurologic deficit In the latter circumstance often the patient will remain alert

Other conditions which may exist include coarctation of the aorta and polycystic disease of the *kidneys*

Intracranial hemorrhage from a nonaneurysmal vascular malformation is a tenable diagnosis under the following circumstances (1) repeated subarachnoid hemorrhages (sometimes more than five) (2) stroke in a young patient with bloody cerebrospinal fluid in the absence of hypertension (3) *antecedent periodic headaches* or epilepsy often with transient postictal paralysis (4) presence of a cranial bruit (5) calcification in the region of the lesion in x ray of the skull

For a discussion of the other causes of intracranial hemorrhage (hemorrhage into primary and secondary brain tumors hematologic disorders *hemorrhage into hemorrhagic* infarction septic

embolism etc) see Chap 145 and pp 1201 1209 The existence of acute leukemia aplastic anemia thrombopenic purpura or cirrhosis of the liver favors the diagnosis of intracranial hemorrhage due to hemorrhagic disease especially if other hemorrhagic manifestations are present

LABORATORY METHODS OF DIAGNOSIS

A number of special laboratory tests are of value in the diagnosis of cerebrovascular disease but none of them can approach in general usefulness a careful history and physical examination The importance of lumbar puncture has already been mentioned If a fine needle is used No 20 and jugular veins are not compressed there is probably little danger in doing a spinal tap in most cases Nevertheless the procedure should not be routine in every case a decision should be reached at the time of the first examination as to the necessity of the procedure and as to the most appropriate time If cerebellar or temporal lobe herniation is threatening the lumbar puncture may contribute to a fatal issue and should be deferred unless absolutely necessary This is especially so in brain hemorrhage massive cerebral infarction cerebellar infarction and hypertensive encephalopathy In primary subarachnoid hemorrhage the lumbar puncture although necessary for diagnosis should not be repeated except to investigate the possibility of further hemorrhage or in order to alleviate severe headache It is not advisable to attempt to remove the blood in the cerebrospinal fluid by repeated punctures

Many cases of apoplexy should have x rays of the skull en route to a hospital bed especially if there is any suspicion of trauma The finding of unexpected fractures a displaced pineal gland or calcification in an aneurysm or vascular malformation will be helpful in diagnosis X ray of the chest is useful as part of the cardiac examination and sometimes will disclose a pulmonary neoplasm or a dissecting aortic aneurysm

Blood cell counts also provide useful information A high hematocrit suggests that polycythemia is a factor a severe anemia and greatly increased sedimentation rate might provide a clue to the existence of subacute bacterial endocarditis and should lead to a blood culture Leukemia and thrombopenia of course must be diagnosed from the blood examination In aneurysmal ruptures there may be a transient albuminuria and hyperglycemia with glycosuria Hypertensive hemorrhage too can cause hyperglycemia Serologic tests for syphilis should be done on the blood and spinal

electrocardiogram should be obtained in all cerebral infarction Occasionally it will presence of a recent silent myocardial

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infarct or provide correlative evidence of hypertension An electroencephalogram is abnormal in most major strokes and is a useful means of following the course of the illness However its utility in the diagnosis of cerebrovascular diseases has yet to be determined

Carotid arteriography is indispensable in the diagnosis of aneurysms and vascular malformations Some 75 to 80 per cent of such lesions within the territory of the carotid arteries are revealed by this method It carries some risk always and the authors have not in the past favored its use in cerebral infarction except in a few cases of suspected occlusion of the internal carotid artery With recent interest in vascular surgery of the carotid system *arteriography* will have to be used with increasing frequency Retinal arterial pressure measurements have also been of help in detecting occlusion of the internal carotid artery

CONCLUSION

Of all the forms of neurologic disease those described in this chapter are of the greatest importance to the practicing physician The assiduous application of clinical method and laboratory test will permit diagnosis of the type of cerebrovascular disease with approximately 75 per cent accuracy enabling the physician to use sensible therapeutic measures in many of the cases Future developments it is hoped will improve both the accuracy of diagnosis and the effectiveness of therapy

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255 TRAUMATIC DISEASES OF THE BRAIN AND SPINAL CORD

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TRAUMATIC DISEASES OF THE BRAIN

Head injury which is the basis of some of the most frequent and serious neurologic disorders in these times of high velocity transport and mechanization in industry poses many problems to the practicing physician To deal with them effectively demands a knowledge of the clinical manifestations as well as a sound grasp of fundamental physiologic mechanisms The physician must stand prepared at all times for he may at any moment be summoned to render aid or to assess the clinical status of a person who has suffered an injury of the head or spine The present chapter undertakes to review the salient facts concerning these injuries of the nervous system and to outline an approach to these problems that has been useful to the authors

Physiologic and Pathologic Considerations

The very language with which certain types of head injury are discussed divulges a number of misconceptions that have been inherited from previous generations of physicians Words have crept into medical vocabulary and have often been retained long after the ideas for which they stood have been refuted—clear evidence of the disadvantage of prematurely adopting explanatory rather than descriptive terms The word *concussion* for example implies the violent shaking and agitation of an organ or the functional impairment which results therefrom Yet despite numerous experiments intended to demonstrate these physical changes within nerve cells (vibration effects formation of intracellular vacuoles etc) no confirmation of their existence has been possible Similarly the word *contusion* meaning a bruising or crushing without interruption of physical continuity is applied rather indiscriminately to a variety of clinical states some of which could not depend on a pathologic change of this type e g minor contusion state or syndrome"—an expression introduced by Wilfred Trotter who was himself most critical of words that embalm a fallacious theory

In all attempts to analyze the mechanism of brain damage in head injury one fact stands preeminent—that there must be the sudden application of a physical force of considerable magnitude to the head Unless the head is struck the brain suffers no injury—except in the rare and somewhat controversial cases of crush injury to the chest or explosive injury with raised intrapulmonary pressure in which petechial hemorrhages are said to have been found in the brain A second fact also susceptible of easy verification is that the size of the area on the skull over which the force is exerted is of importance High velocity missiles destroy a small part of the skull and penetrate the cranial cavity without significant displacement of the head or brain and heavy crushing injuries which result from the skull being compressed between two converging objects may crush the brain In these two circumstances it is interesting to note that the patient may suffer severe and often fatal injury without immediate loss of consciousness Hemorrhage destruction of brain tissue and if the patient survives for a time meningitis or abscess are the principal pathologic changes created by injuries of this type They offer little difficulty to understanding

The common civilian injury is one in which a rapidly moving blunt object strikes the head or the head is flung against a hard surface Injuries of this type often termed *blunt head injuries* are remarkable in two respects (1) they almost always induce at least a temporary loss of consciousness (2) even though the skull is not penetrated and fragments of bone are not driven into its cavity the brain may suffer gross damage i e contusion laceration hemorrhage swelling herniation etc Clinicians as well as experimental physiologists have sought a theory which would bring into plausible form all gross neuropathologic changes the skull fracture and the transient paralysis of nervous function (concussion) or prolonged coma so often observed in fatal cases It may be said that a comprehensive theory acceptable to all workers in this field has not been developed as yet

The relation of skull fracture to injury of the cerebral tissues has been viewed in changing perspective through the entire history of this subject In earliest times fractures dominated the thinking of the medical profession and cerebral lesions were regarded as secondary Some of the best articles on the location of fractures and their relationship to anatomic peculiarities of the cranial bones were written in the eighteenth and nineteenth centuries Later it became known that the skull although rigid is still flexible enough to yield to a severe blow without fracture Therefore the presence of a fracture although a rough measure of the violence to which the brain has been exposed is not an infallible index and even in fatal head injury autopsy may reveal an intact skull in 20 to 30 per

cent of cases Also many patients suffer skull fracture without serious disorder of cerebral function

The modern trend is to be interested more in the presence or absence of brain injury than in the fracture of the skull itself Nevertheless fractures cannot be dismissed without a few comments for they assume importance in indicating the site and possible severity of brain damage in providing an explanation for cranial nerve palsies and in affording potential pathways for the ingress of bacteria and air or the egress of cerebrospinal fluid

The existence of a basal skull fracture may be indicated by *signs of cranial nerve damage* Cranial nerves which are particularly liable to injury are the olfactory optic oculomotor first and second branches of the trigeminal the facial and the auditory Anosmia and an apparent loss of taste (actually a loss of aromatic flavors elementary tastes—salt sweet bitter sour—being retained) are frequent sequelae of head injury especially of falls on the back of the head In the *majority* of cases the anosmia is permanent or the patient may have some perversion of smell (parosmia) The anosmia may be unilateral and not noticed by the patient The mechanism of these disturbances is believed to be displacement of the brain and tearing of the olfactory nerve filaments A fracture in or near the sella may tear the stalk of the pituitary gland with resulting diabetes insipidus A fracture of sphenoid bone may lacerate the optic nerve with complete blindness from the beginning The pupil is dilated and unreactive to a direct light stimulus but still takes part in the consensual reflex The optic disk becomes pale i e atrophic after an interval of several weeks Partial injuries may result in a troublesome blurring of vision Injury to the eighth cranial nerve with petrosal fractures causes loss of hearing and/or dizziness immediately after injury The deafness due to nerve injury must be distinguished from that caused by rupture of the eardrum or the presence of blood in the middle ear and the vertigo from posttraumatic giddiness In oculomotor nerve injury there is a divergent squint with loss of internal and vertical movement of the eye and a fixed dilated pupil Diplopia only on looking down suggests trochlear nerve affection Direct injury of the facial nerve by a basal fracture may be present immediately after the injury or may be delayed coming on after several days This delayed form is usually transitory and its mechanism is not known It may be misinterpreted as an important progression of the traumatic intracranial lesion Injury to the ophthalmic or maxillary divi*sions of the trigeminal nerve may* be the result either of a basal fracture across the middle cranial fossa or of a direct extracranial injury to the branches of these nerves Numbness and paresthesias over the area of skin supplied by the nerve or a troublesome neuralgia are the sequelae of these injuries

If the skin is lacerated over the skull fracture and the underlying meninges are torn or if the fracture *passes through the posterior wall of a nasal sinus* bacteria or air may enter the cranial cavity (meningitis abscess aerocele) Cerebrospinal fluid may also leak into the sinus and present as a watery discharge from the nose (cerebrospinal fluid rhinorrhea) Persistence of the rhinorrhea or the occurrence of episodes of recurrent meningitis (headache convulsions fever and stiff neck with pleocytosis *and sometimes bacteria) are often indications for* a repair of the torn dura mater over the fissure Depressed fractures are of significance only if the underlying dura is lacerated by spicules of bone or the brain is compressed

Much has been written about the mechanism of coma in closed or blunt head injury Two facts concerning this condition stand out clearly (1) it *bears no relationship to skull fracture* (2) the optimal conditions for its production are those in which there is some change in the momentum of the head i e movement is suddenly imparted to it by a blow or its movement is suddenly arrested Striking the stationary head of an experimental animal will cause a loss of brain stem reflexes only if the head was free to move not if it is clamped in one position (Denny Brown and Russell) This finding alone would stand in refutation of such theories of concussion as a wave of high intracranial pressure due to the indentation of the skull or a subsequent wave of negative pressure (Kahn Ward and Clark) cerebral anemia (Trotter) or a general vibration or agitation transmitted via the skull The speed of acceleration or deceleration of the head necessary for this concussive effect must exceed 28 ft per sec The initial action of the blunt injury of this type is to excite the nervous system (the stars that one sees with a minor injury the gasp of the animal) and this is followed by transient paralysis of cerebral function i e abolition of consciousness suppression of reflexes arrest of respiration etc The means whereby the latter effects are produced is not known The old studies of Fischer and Alquie show that in most head injuries there is displacement of the brain within the skull The brain being suspended in a water jacket of cerebrospinal fluid tends not to follow movements of the cranium but to lag because of its own inertia The superior parts of the cerebral hemispheres are free to move more than the lower parts which are *attached to the relatively fixed* brain stem There is the possibility then of stretch or torsion on midbrain and subthalamic structures and indeed temporary paralysis of the reticular activating mechanism which is located in these parts of the brain has recently been demonstrated

This could account for both the unconsciousness and suppression of reflexes and also the electroencephalographic changes (relative electrical silence followed by slow waves) It would appear however that the cerebrum itself does not escape damage for Meyer and Denny Brown have found evidence of an electrical injury potential and reduction in oxygen uptake in the cerebral cortex The changes *whatever and wherever they may be are for the* most part transitory and would be expected to have no visible structural basis Pathologic changes such as have been described in several published accounts of experimental concussion are difficult to evaluate The report of diffuse degeneration of the cerebral white matter in rabbits and monkeys which were repeatedly struck on the head (Jakob) the observation of petechial hemorrhages in the cervical cord and medulla in the cat dog and monkey (Denny Brown and Russell) and the demonstration of chromatolysis of large nerve cells in the brain stem of concussed animals (Windle et al) have not been verified It is unlikely that any of them could be the pathologic basis of the concussive state

In fatal cases of severe head injury where this concussive injury *must also have existed the brain* is almost invariably bruised or lacerated and often there is hemorrhage either meningeal or intracerebral *The observation of these gross pathologic* findings had led to the widely prevalent view that head injuries are largely matters of bruises and hemorrhages and of urgent operations That this can hardly be the case is suggested by the fact that some patients survive head injuries almost as severe as the fatal ones and yet make an excellent recovery At autopsy years later old contusions (*plaques jaunes*) and hemorrhages of approximately the same distribution and extent as those observed in some of the immediately fatal cases are found One can only conclude therefore that most of the immediate symptomatology of severe head injury both *general and localized depends on invisible* and highly reversible change in the brain probably of the same nature as that which underlies concussion Nevertheless these bruises lacerations hemorrhages and localized swellings of tissues cannot be disregarded because they are probably responsible for many of the fatalities that occur 12 to 72 or more hours after the injury Of these lesions the most important is the surface bruising of the brain beneath the point of impact (coup injury) and the more extensive lacerations and contusions on the opposite side of the brain (contrecoup injuries) The inertia of the brain which causes it to be flung *against the side of the skull that was* struck and to be pulled away from the contralateral side has been invoked to explain these coup contrecoup contusions This theory has been further elaborated by Holburn who points out that the brain is roughly spherical and that all movements of the head describe an arc with its axis at the *point of attachment of skull to spine Sudden* changes in the momentum of the head therefore induce a swirling motion to the brain which may *then suffer injury against all rough bony prominences* (wings of sphenoid bones petrous parts of temporal bones rough surfaces of orbital and frontal bones) The lacerations and hemorrhages are based on a similar mechanism the latter being due merely to the tearing of larger vessels Also extensive infarction of the brain may occur when cerebral arteries are compressed between a herniating mass of brain and the dura e g the posterior cerebral artery in temporal lobe herniations An important fact from the standpoint of the clinician is that these contusions hemorrhages and extensive necrotic lesions whatever their mechanism may be may occur without a penetrating head injury and under these circumstances they and their clinical effects are engrafted upon the traumatic paralysis of cerebral function which is called *concussion* They are in a sense epiphenomena which nonetheless may unfavorably tip the balance of life and *death The most compelling evidence of the correctness* of this view is that head injury may end fatally without any visible structural change in the nervous system However *in most fatal cases a* significant degree of bruising edema hemorrhage and herniation is also present

Clinical Manifestations of Head Injury

The physician upon being called to see a patient who has had a head injury will generally find him in one of three clinical conditions each as Trotter Symonds and Rowbotham have pointed out must be dealt with differently It is usually possible to place the patient in one of the following three categories by determining the degree of unconsciousness at intervals of time after the accident *and by assessing the mental* and general neurologic status when the patient is first seen

Patients Who Are Conscious or Are Rapidly Regaining Mental Clarity When *First Seen (Minor* Head Injury) The typical example is a patient who was rendered unconscious by a knock on the head and then regained his senses within seconds minutes or hours Roughly two degrees of disturbance of consciousness may have occurred First there is the patient who was never unconscious at all He was observed to have struck his head and was stunned or saw stars By all criteria his head injury was insignificant when judged in terms of *life and death* and severe brain damage though in exceptional cases there is always the possibility of skull fracture or epidural or subdural hematoma Nevertheless a troublesome *group of symptoms* may have developed at once or within a few days The

patient may begin to complain of headache dizziness loss of confidence in himself inability to concentrate nervousness poor sleep fatigue and depression The headache is of a pressing aching type and is characteristically worsened by any physical and mental effort stooping and excitement No clue is provided as to the mechanism of these symptoms The possibility that these symptoms represent a traumatic or *compensation neurosis* is suggested because of the purely subjective nature of the symptoms and lack of abnormal neurologic signs and the absence of change in cerebrospinal fluid or alteration of the EEG In recent years a better appreciation of the constancy of this clinical syndrome has favored the view first put forward by Wilfred Trotter that they are the direct physical effects of injury incorrectly designated by him *minor cerebral contusion* state The severity of these symptoms is not clearly related to the severity of the head injury Their persistence constitutes a most vexatious therapeutic problem

If consciousness was temporarily abolished the patient is said to have suffered a *concussion* defined by Trotter as an essentially transient state due to head injury which is instantaneous in onset manifests widespread symptoms of a purely paralytic kind does not as such comprise any evidence of structural cerebral injury and is always followed by amnesia for the actual moment of the impact The patient if observed immediately after the injury shows a complete paralysis of nervous function In a few instances death has occurred at this time from respiratory arrest or cardiac arrhythmia and no lesion was found at post mortem examination However the usual sequela is for the pulse and respiration (if they were depressed or arrested) to return at once and for muscle tone reflexes voluntary movement and mental clarity to be regained within a few minutes Only an amnesia for the accident and the events that immediately preceded (retrograde amnesia) and followed it (anterograde amnesia) will remain Thereafter the patient may suffer the same headaches giddiness and nervousness described above

These relatively trivial head injuries may be the source of a number of other puzzling features (1) *Delayed traumatic collapse* following an accident a few patients after walking about and seeming to be mentally normal will turn pale and fall unconscious for a few minutes This is a vasomotor syncopal attack and is probably related to injury pain and emotional upset Rarely do they exhibit any focal or lateralizing neurologic signs The suggestion that this represents medullary edema is hardly tenable (2) *Immediate traumatic paraplegia* with falls on top of the head which may injure the motor areas for the lower extremities both legs may become temporarily weak and numb sometimes with bilateral Babinski signs and sphincteric incontinence Concussion of the cervical segments of the spinal cord is another possible mechanism of this paraplegia (3) *Immediate hemiplegia* or *monoplegia* these conditions may develop immediately after a minor injury with or without blood in the cerebrospinal fluid and are commonly attributed to a relatively circumscript injury with *minimal concussion and a direct contusion or laceration* of the underlying brain (cerebrospinal fluid is sanguineous) (4) *Immediate traumatic epilepsy* a series of focal seizures may occur with a minor bruise of the cortex and may be followed by a postepileptic paralysis of short duration (5) *Delayed hemiplegia or monoplegia in interval paralysis* in cases of minor or major injury usually signifies an epidural hemorrhage a subdural hemorrhage or hygroma arterial thrombosis spreading venous thrombosis or intracerebral hemorrhage (6) *Acute drowsiness confusion* and *headache* or *coma* due presumably to localized and generalized traumatic brain edema children who have had concussion are especially liable to headache drowsiness and vomiting which may have its onset some hours after the *injury* In these children infusions and clyses of water and 5 per cent glucose are particularly dangerous such treatment may prove fatal owing to a water intoxication and severe brain swelling Apparently an excessive output of antidiuretic hormone and water retention occur under these circumstances

Patients Who Are and Have Been Unconscious Since the Time of the Accident (Major Head Injury) ***The Clinical State*** In this group which includes the patients with the more severe head injuries the outlook is obviously less favorable and one is concerned at first for their life However within this group there is still a wide variation in the severity of the traumatic brain disease A certain number of patients die at once or within a few minutes and it may be assumed that the direct injury to the brain or some other organ was incompatible with life Other patients in this group recover consciousness rapidly after several hours but a few remain deeply comatose for days or even weeks The mortality rate in those who reach a hospital in coma is approximately 20 per cent and most of them die within the first 12 to 24 hr Of those alive after 24 hr the mortality is 7 to 8 per cent and after 48 hr the figure falls to 1 per cent

In the patient whose prognosis is favorable the coma is less deep (stupor semicoma or confusion —see Chap 33) For a time he may be restless and difficult to control The reflexes are normal as are pulse blood pressure and respiration He is able to swallow and may or may not speak There are no obvious neurologic signs In contrast those patients whose illness will end fatally may be moribund

from the beginning Their coma is profound The limbs may be flaccid and without reflexes The corneal and pharyngeal (gag) reflexes are absent The pupils are small and unreactive to light or dilated and fixed or unequal The ocular axes are divergent or askew The jaw sags the tongue falls back in the throat saliva drools from the mouth and swallowing is obviously lost There may be surgical shock at first for a brief period with the usual findings of pale and moist skin weak and rapid pulse subnormal temperature and a blood pressure that is difficult to obtain Within a few hours however the temperature usually rises and this may continue until death The breathing may be stertorous and later feeble and irregular The state of consciousness and the temperature chart provide information of great value in appraising the status of the patient An ascending pulse rate possibly interspersed by short periods in which there is a bounding slow pulse and rising temperature or a combination of fast pulse and subnormal temperature are signs of a grave prognosis

In the group of patients whose outlook is less bleak deep coma soon gives way to semicoma The blood pressure stabilizes and the temperature and pulse having risen to 101 to 102 F and 100 to 110 respectively remain at these levels Muscular tone is regained in the limbs and the tendon reflexes are present This is a critical period for a sudden rise in temperature cyanosis and increasing respiratory difficulty may result in a fatal issue Once the patient regains consciousness sufficiently to respond to a spoken command the physician no longer needs to be concerned about survival and may begin to think about the possibility of focal brain damage and prospects for recovery There is still a substantial risk in the first 2 or 3 weeks however from pneumonia meningitis or epidural and subdural hemorrhage which may intervene and impair the chances of survival It is often said that death during the first 12 hr is the result of the direct injury of the brain that which occurs later is usually the result of some complication of cranial trauma (intracerebral or subarachnoid hemorrhage herniation of the temporal lobe localized or generalized edema epidural or subdural hemorrhage meningitis pneumonia)

The course of clinical events in those who survive the first 24 to 48 hr is much like that in patients with type I injury except that it is likely to be more prolonged As coma lessens the patient opens his eyes he may pause in his restless activity and seem to listen to what is said He reacts briskly to painful stimuli applied to the face passive manipulations of the head and pinching the inner surface of the arms or legs Moaning and groaning are the first vocal activities to return their absence in patients who are beginning to respond always suggests aphasia Restlessness irritability and hyperactivity may assume such proportions that the patient must be restrained For example he may resist all attempts to help him struggle against restraints yell talk incessantly and without sense strike at everyone near the bed etc This state sometimes called *traumatic delirium* may last hours or days but eventually is replaced by a more quiet confusional state Then the patient speaks unless aphasic and is variably able to engage in conversation His thinking processes are slow and inefficient and his thoughts are likely to be incoherent Often he cannot understand the purposes of his splints bandages catheters etc and will remove them even when asked repeatedly not to do so Movements and reactions to stimuli are more or less automatic and if conversation is possible it is repetitious and often incoherent Also memory is obviously faulty As confusion lessens there may be a brief period when mental function is nearly normal yet later there will be little or no memory for what transpired From a close study of this clinical sequence it is obvious that the capacity to form retain and reproduce new experiences is one of the best tests of the mental status Not until the patient reaches the stage of continuous anterograde memory will he regard himself as fully normal In looking back upon this period the patient can recall only a few events and has the impression that he was unconscious all this time Retrograde amnesia for the accident and for the events which preceded it which often extends over a period of minutes hours or even days is another invariable accompaniment of severe head injury This period of retrograde memory defect shortens as convalescence proceeds

Focal and lateralizing neurologic symptoms and signs as would be anticipated will be observed with notable frequency in this group of patients These abnormalities are presumably related to hemorrhage and contusion and in as much as they are usually engrafted on a severe concussive injury they become manifest as consciousness is regained Local injury to the brain without a disturbance of consciousness occurs exceptionally and then more often with the penetration of the skull by missiles or a direct or glancing blow by a relatively small object (golf ball stone) sometimes with depression fractures Of the focal symptoms hemiparesis is probably the most frequent The weakness of arm and leg may be evident even during coma by the hypotonia the less frequent movement of the limbs inequality of tendon reflexes and a more persistent Babinski sign on one side Complete hemiplegia is rarely observed Hemihypesthesia although occasionally found is less common possibly because sensory tests are difficult to interpret until mental clarity is regained Homonymous hemi

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Acute and Chronic Subdural Hematoma The problems created by the acute and the chronic subdural hematoma are so different that they must be discussed separately In *acute subdural hematomas* which may be unilateral or bilateral the latent interval is usually longer than in epidural hemorrhage—many days or 1 to 2 weeks Headaches drowsiness sometimes agitation slowness in thinking and confusion which progressively worsen are the most frequent symptoms Focal or lateralizing signs (hemiplegia) are late and tend to be less prominent than the disturbance of consciousness Frequently the acute subdural hematoma is combined with cerebral contusion and laceration so that the clinical effects of these several lesions are difficult to distinguish and there are some patients in whom it is impossible before operation to state whether the surface clot is epidural or subdural in location The treatment is bilateral temporal burr holes and thus is also one of the most certain diagnostic procedures If the clot that is found is too small to explain the symptoms the surgeon usually proceeds to do a right subtemporal decompression

In chronic subdural hematoma mentioned in the differential diagnoses in Chaps 36 254 and 256 the traumatic etiology is less clear The head injury especially in the elderly person may be trivial (striking the head against a branch of a tree or on the mantel of a fireplace during a faint etc) or it may have been forgotten completely A period of weeks then follows when headaches (not invariable) giddiness slowness in thinking confusion exaggeration of certain personality traits and rarely a seizure or two are the main symptoms The initial impression may be that the patient has a brain tumor a drug intoxication or a depressive senile or other psychosis As with acute subdural hematoma the disturbance of consciousness (drowsiness inattentiveness incoherence of thought stupor or coma) is more prominent than focal or lateralizing signs The latter usually consist of hemiparesis and rarely of an aphasic disturbance Hemianesthesia and homonymous hemianopia are seldom observed probably because the anatomic structures subserving these functions are deep and not easily compressed (in the case of hemianopia) and sensory changes are likely to be overlooked in a stuporous confused patient Hemiplegia i e complete paralysis of one arm and leg is usually indicative of an intracerebral lesion rather than of a compressive surface lesion Another important feature of the hemiparesis is that it may be contralateral or ipsilateral depending on whether or not herniation of the temporal lobe through the notch of the tentorium into the posterior fossa and compression of the contralateral cerebral peduncle are present if they are present pyramidal signs are then ipsilateral to the clot or bilateral As the condition progresses the patient becomes comatose but often with striking fluctuations of awareness The ipsilateral pupil dilates (Hutchinson s pupillary sign) owing it is believed to direct pressure of the herniating temporal lobe upon the oculomotor nerve The dilated pupil and a ptotic eyelid are more reliable indicators of the side of the hematoma than the hemiparesis though they too can be misleading in certain cases Convulsions are usually seen only in alcoholics or cases with a contusion and cannot be regarded as a cardinal sign of subdural hematoma even though they are not infrequent Roentgenograms of the skull are usually negative except for a shift of a calcified pineal to one side or an occasional unexpected fracture line The EEG is usually bilaterally abnormal sometimes with reduced voltage or electrical silence over the subdural hematoma or high voltage slow waves over the same and opposite sides because of the damping effects of the clot and displacement of the brain The anterior and middle cerebral arteries are seen to be displaced in an arteriogram The cerebrospinal fluid may be clear bloody or xanthochromic depending on the presence or absence of recent or old contusion and subarachnoid hemorrhage and the pressure may be elevated normal or subnormal Of all these diagnostic procedures direct burr hole exploration is the most reliable

The acute rapidly evolving subdural hematomas are due to tearing of bridging veins and direct compression of the brain by an expanding clot of fresh blood Unlike the epidural arterial hemorrhage which is progressive the bleeding is usually arrested by the rising intracranial pressure The chronic subdural hematoma is believed to cause symptoms by becoming encysted by fibrous membranes (pseudomembranes) which grow from the dura In its encysted state as red corpuscles hemolyze and blood proteins disintegrate the osmotic pressure rises and fluids enter the hematoma with the result that the hematoma enlarges and the compressive effects increase Severe cerebral compression and displacement with temporal lobe–tentorial herniation are the usual causes of death

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Laboratory Findings In this group of patients with severe head injury there is a high incidence of skull fracture The cerebrospinal fluid is usually sanguineous (red blood cells usually 100 000 per cubic millimeter or less) and under elevated pressure (between 200 and 300 mm) in the majority of patients The prognosis is distinctly less good in those *with more than 100 000 red cells per cubic* millimeter and pressures in excess of 300 mm Nevertheless death may occur in patients who have no skull fracture a subnormal intracranial pressure and relatively clear cerebrospinal fluid The EEG regularly shows focal and diffuse abnormalities

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Patients Who Are Unconscious When First Seen but Who Are Said to Have Been Conscious after the Accident (Presence of Lucid Interval) This group of patients is smaller than the other two but is of great importance because it includes many who are in urgent need of surgical treatment The initial coma may have been brief or there may have been none at all in which instance one may conclude that there was neither concussion nor contusion The following conditions must be considered in every case of this type

Acute Epidural Hemorrhage This condition is due as a rule to a temporal or parietal fracture with laceration of the middle meningeal artery and vein Less often there is a tear in a dural venous sinus The injury even when it fractures the skull *may not have produced coma A typical example is* a child who has fallen from a bicycle or a swing or has suffered a hard blow to the head in a fight and was only momentarily unconscious A few hours or a day or two later (the interval may be as long as several days or a week especially with venous bleeding) he develops headache of increasing severity vomiting drowsiness confusion seizures which may be one sided hemiparesis with slightly increased tendon reflexes and Babinski sign As coma develops the hemiparesis with Babinski sign may give way to flaccid or spastic limbs and Babinski signs bilaterally There may be aphasia Respirations become deeper and stertorous then shallow and irregular and finally stop The pulse is often slow (below 60) and bounding with a concomitant rise in systolic blood pressure The pupil may dilate on the side of the hematoma The cerebrospinal fluid is usually under increased pressure though normal and subnormal pressures do not exclude the possibility of an epidural hematoma The fluid may be clear or sanguineous depending on whether or not there is an associated contusion laceration or subarachnoid hemorrhage Death which is almost invariable if the clot is not removed surgically comes at the end of a comatose period rarely if ever in a conscious patient and is due to respiratory arrest The visualization of a fracture line across the groove for the middle meningeal artery and a knowledge of the side of the head struck (the clot is usually on that side) are of aid in diagnosis and of lateralization of the lesion

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Acute Epidural Hemorrhage This condition is due as a rule to a temporal or parietal fracture with laceration of the middle meningeal artery and vein Less often there is a tear in a dural venous sinus The injury even when it fractures the skull may not have produced coma A typical example is a child who has fallen from a bicycle or a swing or has suffered a hard blow to the head in a fight and was only momentarily unconscious A few hours or a day or two later (the interval may be as long as several days or a week especially with venous bleeding) he develops headache of increasing severity vomiting drowsiness confusion seizures which may be one sided hemiparesis with slightly increased tendon reflexes and Babinski sign As coma develops the hemiparesis with Babinski sign may give way to flaccid or spastic limbs and Babinski signs bilaterally There may be aphasia Respirations become deeper and stertorous then shallow and irregular and finally stop The pulse is often slow (below 60) and bounding with a concomitant rise in systolic blood pressure The pupil may dilate on the side of the hematoma The cerebrospinal fluid is usually under increased pressure though normal and subnormal pressures do not exclude the possibility of an epidural hematoma The fluid may be clear or sanguineous depending on whether or not there is an associated contusion laceration or subarachnoid hemorrhage Death which is almost invariable if the clot is not removed surgically comes at the end of a comatose period rarely if ever in a conscious patient and is due to respiratory arrest The visualization of a fracture line across the groove for the middle meningeal artery and a knowledge of the side of the head struck (the clot is usually on that side) are of aid in diagnosis and of lateralization of the lesion

Epilepsy Posttraumatic epilepsy which occurs in 20 to 40 per cent of patients is one of the most dreaded complications of head injury Its basis is nearly always a contusion or laceration of the cortex The likelihood of epilepsy is said to be greater in parietal and posterior frontal lesions but it may arise from lesions in any area of the cerebral cortex The incidence of epilepsy is much greater in open than in closed head injuries Indeed in cases of pure concussion without contusion or laceration seizures are not much more frequent than in the general population The interval between the head injury and the first seizure averages about 9 months but it may be much longer particularly in children The longer the interval the less certain one is of its relationship to the traumatic incident There is a slightly greater tendency for those patients who had seizures at the time of head injury to become subject to recurrent seizures later The seizures are always of focal character or grand mal petit mal is rarely if ever due to trauma The significance of the different patterns of focal seizures which varies according to the location of the lesion has been worked out in detail by Penfield and his associates (see Chap 35) and by Russell et al The frequency of seizures in any given patient varies widely some patients have only a few others many with episodes of status epilepticus The EEG is of value in diagnosis a focus of spike or sharp waves is the characteristic finding Usually the seizures can be controlled by anticonvulsant medications and only the recalcitrant cases are likely to require excision of the epileptic focus The surgical results vary according to the methods of selection and technique of operation Seizures are abolished in less than 50 per cent by excision of the focus

Impairment of Mental Function Fortunately this is a rare sequela to head trauma Although mental function may be disturbed by focal lesions which produce dysphasia agnosia apraxia etc intellectual functions and memory are usually preserved This is true of even the most severe head injuries and is understandable when one considers the relatively small amount of brain tissue destroyed by the traumatic process The only exceptions to this statement are the few patients who survive a severe compression of the midbrain by a herniating temporal lobe and those with extensive degeneration of the cerebral white matter Children previously of low average or borderline intelligence and the aged who unnoticed had developed senile mental changes constitute other exceptions The aging person may have worked and functioned reasonably well until the time of the injury and afterwards is found to have a grave impairment of memory thinking and emotional control that permanently disables him That this is not simply a traumatic effect is indicated by the fact that the severity of the mental defect does not seem to parallel the severity of the head injury and as the months and years pass the mental disorder may progress (the natural course of brain trauma is one of sudden onset with maximal functional disturbance within minutes or hours and then improvement) This is one of the reasons why the prognosis in elderly adults is less good than for younger individuals

Posttraumatic Nervous Instability Undoubtedly the most troublesome sequela of head injury is that alluded to in the discussion of group 1 cases—*headache giddiness* and *nervous instability* This has been called the *postconcussional syndrome* or the *minor contusion syndrome* or *posttraumatic vasomotor neurosis* (Friedmann) All these terms are objectionable on the grounds that they suggest an explanatory hypothesis as yet unproved Headache is the central symptom usually at times localized to the part struck It is variously described as an aching throbbing pounding stabbing pressing pain and is remarkable for its variability The intensification of symptoms by mental and physical effort straining stooping and emotional excitement has already been mentioned Rest and quiet may relieve it Thus it becomes a major obstacle to convalescence which demands always a resumption of normal activities The dizziness is usually not a true vertigo but a giddiness The patient feels suddenly unsteady dazed weak or faint However a certain number of patients report symptoms which suggest a labyrinthine disorder For example objects in the environment are said to move momentarily and looking upward or to the side may cause a sense of unbalance Labyrinthine tests may show either hypo- or hyperreactivity or the results may prove to be normal The data are usually so indefinite that it is impossible to state whether or not the labyrinth and vestibular mechanisms have been injured Exceptionally vertigo is accompanied by diminished excitability of both the labyrinth and the cochlea and one may assume the existence of direct injury to the nerve or end organ The giddy patient usually is intolerant of noise emotional excitement and crowds Tenseness restlessness inability to concentrate a feeling of nervousness fatigue worry apprehension and an inability to tolerate the usual amount of alcohol complete the clinical picture In contrast to the multiple subjective symptoms detailed tests of intellectual functions and memory show little or no impairment This syndrome once established may persist for months or even years but usually the symptoms lessen as time passes It occurs in both sexes all races and at all ages excepting childhood There has been much controversy over its cause and to the present time its anatomic and physio

Treatment consists of placing burr holes and evacuating the clot before deep coma has developed

Subdural hygromas (collections of blood and cerebrospinal fluid in the subdural space) may also form after an injury as well as after meningitis (in an infant) and pneumoencephalography It is said that a tear of the arachnoid permits the accumulation of cerebrospinal fluid into the subdural space where it becomes trapped The patient may complain of severe headache drowsiness and confusion which are relieved when the subdural fluid is drained

Cerebral Hemorrhage (Immediate and Delayed) Acute massive brain hemorrhages are more frequent in elderly patients than in young ones and are usually fatal within a few hours The clinical picture is similar to that of hypertensive brain hemorrhage (deepening coma with hemiplegia a dilating pupil bilateral Babinski signs stertorous and irregular respirations) Indeed the problem that often cannot be solved even at post mortem examination is whether the patient had a hemorrhagic type of stroke and then fell or a fall that caused the hemorrhage If the bleeding is slow there may be an interval of 2 to 3 days between injury and the symptoms of the oncoming hemorrhage Coma or confusion if present from the time of the injury may obscure the signs of the intracerebral hemorrhage Craniotomy with evacuation of the clot has given a successful result in a few cases

Repeated Concussion (Punch Drunk) The cumulative effects of repeated injuries observed almost exclusively in professional boxers constitute a type of head injury difficult to classify for it has never been well studied pathologically It is a common observation that after a number of years in the ring pugilists often become forgetful slow in thinking and slightly dysarthric Their movements are stiff and uncertain especially those involving the legs there is unsteadiness of gait and occasionally there may be involuntary movements The plantar reflexes may be extensor on one or both sides The electroencephalogram shows slow waves of theta and sometimes of delta type The anatomic basis of this disease is unknown The postulation of showers of petechial hemorrhages from repeated blows on the jaws should not be given credence until demonstrated pathologically The findings of diffuse degeneration of the cerebral white matter in rabbits and monkeys which have been subjected to repeated concussions (Jakob) offer a more acceptable possibility

Sequelae of Severe Head Injury

The signs of focal brain disease whether due to open and penetrating or closed head injuries tend always to ameliorate as the months pass A hemiplegia is often reduced to a minimal hemiparesis or ineptitude of voluntary motor function with exaggerated reflexes and an equivocal Babinski sign on that side and aphasia improves to become a stuttering or hesitant paraphasia which is not disabling except in a professional worker or writer Many of the signs of brain stem disease improve often to an astonishing degree

Protracted Traumatic Coma and Pseudocoma Of particular interest is the outcome of those few patients who remain comatose for weeks or months or even years The authors have examined the brains of nearly a dozen cases of this type and nearly all have shown numerous foci of hemorrhage and ischemic necrosis in the midbrain and subthalamus especially in the tegmentum and tectum These were probably due in most instances to temporal lobe herniation and midbrain compression for one could see where one side of the base and tegmentum had been indented by the free edge of the tentorium In others there may have been direct injury to the midbrain and pons with numerous small hemorrhages Presumably these pathologic changes are not constant for scattered lesions in the cerebral cortex (contusions of the summits of convolutions ischemia with necrosis in the depths of sulci) and a remarkable diffuse degeneration of cerebral white matter have also been observed in cases of this type (Strich) These patients while comatose (i e unreceptive to stimuli and unresponsive) or while in a state of pseudocoma (receptive and capable of signaling by blinking their eyes but otherwise unresponsive) usually exhibit a variety of neurologic abnormalities unequal pupils dilated fixed pupil and oculomotor palsy on one side and hemiplegia on the other disturbances of gaze bilateral pyramidal paralysis with Babinski signs extensor postures of arm and leg on one side and flexed arm and extended leg on the other brain stem attacks (extension of limbs increased respiration blood pressure and sweating on stimulation of any kind) and involuntary movements (tremor chorea athetosis) Some remain in this reduced mental state until death (nearly 10 years in one of the authors cases but usually a few months or a year or two) The majority however may regain enough function to leave the hospital a few surprising as it may seem are restored to full alertness and adequate mental function Residual weakness of limbs slurred speech ocular palsies ataxia of an arm or leg or involuntary movements are frequent During convalescence language mechanisms may be disturbed in various ways There may be mutism akinesia or adynamia (lack of volition or impulse to speak or move) dysarthria and if there are contusions of the cortex of the dominant hemisphere an aphasia as well Any one or a combination of these abnormalities may be present

tained and recorded Verbatim statements should be *written down whenever possible*

The treatment problems presented by each of the three groups of clinical cases discussed above are as follows

Minor Head Injury In this group are included patients who (1) were never unconscious at any time (2) were briefly unconscious but are mentally clear at the time of the first examination (3) are rapidly regaining consciousness

Circumstances dictate how each case is managed If the injury was trivial and the scalp was not lacerated and if the patient is entirely clear mentally little or nothing need be done When the patient is unable to give an accurate account of what has happened and appears still to be somewhat confused or incoherent he should be compelled to lie down or at least remain in one place It often happens that the confusion is not detected and the patient is permitted to resume activity while still acting in an irrational manner He may get into his car and attempt to drive only to have another accident or he may continue to play a game and make a series of errors

When a conscious or nearly conscious patient is admitted to a general hospital it is tempting to let him go his way Experience teaches caution however *A complete examination* with the patient fully undressed should be carried out It is well if there is any likelihood of litigation to obtain x rays of the skull and an electroencephalogram The question of lumbar puncture will usually depend on how serious the injury was on the prominence of posttraumatic headache etc The patient should probably be detained for a few hours or overnight in order to make sure that he is not merely in a lucid interval The first few hours or days may be spent in the hospital If this cannot be arranged and he is sent home a member of the family should be charged with the responsibility of reporting any important change such as increasing headache vomiting drowsiness confusion or seizure Their occurrence would dictate hospital entry *for further examination* an x ray of the skull and possibly a lumbar puncture A posttraumatic headache and drowsiness may be the first signs of an oncoming epidural or subdural hematoma On the other hand they may reflect only what is presumed to be a localized edema Further observation will usually distinguish between these conditions Observation may be safely continued as long as the patient remains conscious Here one may proceed on the rule that the life of the patient with a head injury is never in jeopardy as long *as he is mentally clear and responsive* The only exceptions to this statement are rare instances of fracture through the foramen magnum with contusion of the inferior surface of the cerebellum and with swelling of tissue and herniation through the *foramen magnum* Two of the authors patients with this condition died unexpectedly after a period of intense occipital headache at a time when they were quite alert The management of posttraumatic headache dizziness and nervous instability which often follow relatively minor injuries to the head will be discussed below A simple fracture without involvement of paranasal sinuses requires no special treatment but is believed to contraindicate vigorous athletic activities *for several months* or a year

Patients Who Are Unconscious When First Seen If the physician arrives on the scene of the accident a hurried examination should be made before the patient is moved in order to determine whether there is dangerous hemorrhage from a laceration of the scalp or other parts of the body and whether there is likelihood of a fracture dislocation of the cervical spine which is occasionally associated with head injury If the patient is in shock with cold clammy skin and feeble pulse he *should be covered with warm blankets* In moving an individual with a potential cervical spine injury the spine should be kept straight at all times and flexion of the neck should be avoided This can best be done by placing sand bags or firm pillows *on either side of the head and warning every* one against neck flexion An even safer method is to place the patient on a stretcher face down and arrange pillows to assure a clear airway Bleeding from the scalp can usually be controlled with a firm pad unless an artery is divided and then a suture becomes necessary

In the hospital where all such patients should be taken the first steps should be to control shock This can usually be done by the application of warmth keeping the head low and leaving the patient alone for a few minutes The shock will usually come under control in a few minutes with or without vasopressor drugs or transfusions Persistent shock is rare in head injury and always raises the suspicion of a ruptured viscera with internal bleeding *extensive fractures* or traumatism of the cervical spinal cord A quick survey will enable one to estimate the depth of coma size of pupils and presence of obvious fractures and if shock is not present, or after the blood pressure has stabilized a more detailed examination can be performed The skull should be carefully inspected and palpated The hair should be cut off around the scalp wound A bogginess of the temporal or postauricular region (Battle s sign) bleeding from the nose or ear extensive conjunctival edema and hemorrhage are useful signs of underlying skull fracture However it *should be remembered* that rupture of the eardrum or a blow on the nose may also cause bleeding from the ear and nose re

logic basis has not been settled The constancy of the symptoms their appearance in individuals who have had no trace of neurosis prior to the accident and their relationship to physical and mental activity have led most neurologists to view this syndrome as a manifestation of a specific morbid process in cranial structures Nevertheless the striking reduction in disability when the physician gives firm reassurance and encourages early rehabilitation leaves little doubt as to the existence of important psychologic mechanisms at least for the maintenance of the symptoms And if compensation is involved the motivation to return to previous activities is still further impaired

Extrapyramidal and Cerebellar Disorders The question of *posttraumatic Parkinson s syndrome* has been discussed many times usually with the general conclusion that a true traumatic parkinsonism does not exist Most patients have merely had paralysis agitans or postencephalitic Parkinson s disease brought to light by head injury The head injury may have been severe or trivial and the course of the illness is usually progressive just as it is in the nontraumatic cases Patients who survive a severe midbrain syndrome manifested in the beginning by protracted coma may have a clinical picture which bears some similarity to Parkinson s syndrome but the presence of ocular palsies nystagmus and unilateral or bilateral pyramidal signs should permit easy distinction One should be equally skeptical regarding the existence of a posttraumatic cerebellar ataxia

Posttraumatic Hydrocephalus Rare examples of posttraumatic hydrocephalus with intermittent headaches vomiting confusion and drowsiness have been reported and autopsy has demonstrated an adhesive basilar meningitis attributed to subarachnoid or ventricular hemorrhage Since a symptomatology like this has been observed occasionally after the rupture of a saccular aneurysm with massive subarachnoid hemorrhage due presumably to blocking of the aqueduct and fourth ventricle by blood clot this mechanism has also been suggested as a possible explanation of traumatic hydrocephalus in patients with cerebral contusion However there are other patients with enlarged ventricles who probably at no time had a significant degree of subarachnoid and ventricular hemorrhage The mechanism of the hydrocephalus in these cases is not known

Posttraumatic Psychiatric Disorders In contrast to nervousness and nervous instability which are common sequelae of injuries of all types posttraumatic psychoses are relatively infrequent Adolph Meyer whose study of traumatic insanity is still a standard reference encountered this type of illness in approximately 1 per cent of admissions to a state hospital Statistics from military files and civilian hospitals show that about 1 of every 100 patients with a head injury exhibits a behavioral change which requires incarceration in a mental hospital (the figure is lower for military head injuries 1 in every 1 000 cases) These terms traumatic psychosis and insanity have been used in various ways which makes any summary of data and opinion difficult From the psychiatric standpoint many of the posttraumatic states already described (traumatic stupor delirium confusion or dementia) would be classified as "defect psychoses" Other physicians use this term as it is used here to designate aberrations of behavior which prevent the patient from resuming his place in society The most distressing psychiatric syndromes have been suspiciousness and paranoid delusions unaccountable outbursts of violent temper sometimes with homicidal or suicidal tendencies progressive hyperactivity delirium and mania and episodes of bizarre behavior with subsequent amnesia reminiscent of temporal lobe seizures Alcoholism may provoke some of these behavioral abnormalities Some of these illnesses are undoubtedly due to residual brain damage in individuals of peculiar personality make up However attempts to account for psychoses of this type by reference to constitutional peculiarities and predisposition laid bare so to speak by head injury have not been convincing They may be said to represent first attempts to find working hypotheses Some patients afflicted with these psychoses remain helplessly disabled In others the outcome has been surprisingly good and the patient after some months in a psychiatric hospital has been able to return to his home and his former job

Clinical Approach to the Patient Who Has Suffered Head Injury Suggested Plan for Management

The physician who undertakes to treat the head injury case must at all times bear in mind that assiduous attention to detail may prove to be lifesaving and that accurate documentation of all diagnostic findings and therapy is desirable if the medical data are later to be used in the arbitration of insurance claims worker s unemployment compensation etc The suggestions which follow can do no more than serve as guides for every patient presents a combination of problems that the physician has not encountered before and may not observe again in identical form

Exact data concerning the patient s medical status before the accident (previous illnesses work and social record emotional stability) the nature and precise circumstances of the accident the duration of retrograde and anterograde amnesia and all that transpired afterwards should be ob

minimize the seriousness of his head injury and to reassure him that he will recover Early rehabilitation should be encouraged It may safely begin as soon as the cerebrospinal fluid becomes clear usually within a few days or 1 to 2 weeks at the most except of course in the rare cases of protracted coma.

Posttraumatic headache giddiness and nervousness are the most difficult symptoms to manage during this period Careful explanation of the symptoms an optimistic prognosis and the institution of a program of graded mental and physical activities to the point of tolerance stand the best chance of restoring the patient to a useful life The patient should be told that he must expect a certain amount of headache and should carry on in spite of it Meprobamate 200 mg t i d is useful for anxiety and a non habit forming analgesic medication should be given for the more severe headaches (Empirin or aspirin) Insomnia may require a barbiturate medication or chloral hydrate at first but they should be discontinued as soon as possible Any litigation that may be involved should be settled within 6 to 9 months To delay settlement usually works against the best interests of the patient. The severity of his injury can be ascertained within this period of time and a longer period of observation only enhances his worries and fears and reduces his motivation to return to work

The prognosis of head injury in good hands is influenced by several variables Elderly patients often remain disabled especially when compensation is involved Young and middle aged adults do better if they are not entitled to compensation (Russell's figures 70 per cent of compensation cases back at work in 18 months 83 per cent of noncompensation cases working at the end of this period) Russell also pointed out that the severity of the injury as measured by the duration of traumatic amnesia was a factor If the period of amnesia was less than 1 hr 95 per cent of cases were back at work within 2 months if longer than 24 hr only 80 per cent had returned to work in 6 months About 60 per cent, however still had symptoms at the end of 2 months and 10 per cent at the end of 18 months

INJURIES OF THE SPINE AND SPINAL CORD

Injury to the spinal cord is not infrequent in both civilian and military life It may be the sole complication of an injury or as indicated above it may be combined with head injury Although the primary consideration is whether the spinal cord or spinal roots have been damaged some reference to the nature of vertebral injury is necessary for an understanding of this type of traumatic disease

Varieties of Spinal Injury

A useful classification of spinal injuries is one which divides them into fracture-dislocations pure fractures and pure dislocations The relative frequency of these types is about 3 1 1 Direct violence to the spine is an uncommon cause of vertebral disruption except for stab and bullet wounds most spine injuries are the result of force "applied at a distance" All three types of injury are produced by a similar mechanism usually a vertical compression of the spinal column to which flexion is almost immediately added The two important variables in the mechanics of vertebral injury are the nature of the bones and the strength direction and point of impact of the force

The Nature of the Vertebral Body As lucidly explained by Jefferson, the vertebral column consists of two parallel, fused cylinders of different structure and serving different purposes The anterior column is comprised of the vertebral bodies and intervertebral cartilages whose general purpose is weight bearing The posterior cylinder is an articulated column of neural arches giving protection to the spinal cord From the neural arches arise a number of transverse and spinal processes which provide for muscular attachment Of these two columns or cylinders the anterior is more compressible being constituted of very little compact and much cancellous bone Thus a compressive force usually causes wedging of a vertebral body and is followed by flexion Wedging or collapse of vertebral bodies is most to be expected where they are high and spongy and separated by thick intervertebral disks i e in the lower thoracic and lumbar spine Wedging is seldom complete in the cervical region because violence to the neck in a vertical direction is not applicable without movement of the spine part of the force of the blow being converted into a movement of flexion

***Strength, Direction* and Point of Impact of the Force** If the injuring body striking the cranium is hard and the velocity is high a skull fracture occurs the elastic quality of the skull absorbing the force of the injury If the injuring body is soft yet heavy the spine and particularly its cervical portion will be the part injured If the neck happens to be rigid and straight and the force is quickly applied to the head, the atlas and the odontoid process of the axis may break If the force is not so quickly applied and removed an element of flexion occurs Flexion movement plus a vertical force constitute the essential factors in fracture-dislocation or pure dislocation These types of injury are most *frequent* in the cervical region.

spectively Fractures of the orbital bones may cause displacement of the eye with resulting diplopia and fracture of the jaws disalignment of the teeth and great discomfort on attempting to open the mouth Careful notes should be made regarding temperature pulse blood pressure state of consciousness pupil size ocular movements corneal reflexes facial movements during grimace swallowing *tone of limb muscles movements of* limbs predominant postures and reflexes Vital signs and consciousness should be checked and recorded by the nurse or physician every 2 hr A proper airway must be maintained The best position for the patient is supine with the head on a pillow and turned to one side If urine is retained and the bladder distended a catheter should be inserted and kept there If coma persists for more than 12 to 24 hr a nasal tube should be passed and fluids and nourishment given by that route Intravenous fluids should be administered slowly and not in excessive amounts even hypertonic glucose may increase oncoming pulmonary and cerebral edema the danger of the latter being especially great in children Lumbar puncture should *be done as soon as practicable for* diagnostic purposes (immediately if bacterial meningitis is suspected) and if the pressure is elevated it should be lowered to 100 to 150 mm Daily lumbar punctures have their advocates and their opponents The authors have tended to use them only if the *pressure is elevated and the patient s* condition is not improving Hypertonic solutions ($MgSO_4$ 90 Gm and water 180 ml) may be given per rectum after a cleansing enema and held for 30 min or if the patient can swallow 60 ml of this solution may be given by mouth every hour until a loose bowel movement is obtained Hypertonic solutions intravenously are of less certain therapeutic value Fifty to one hundred milliliters of 50 per cent glucose or hypertonic sucrose may be injected intravenously if operation is to follow within a few hours but otherwise should probably not be given for there may be an even higher cerebrospinal fluid pressure after their hypertonic effect wears off X rays of skull and other parts should be taken after the first day or two unless there is a suspicion of an epidural hemorrhage in which case they should be made at once to visualize a crack across the course of the middle meningeal artery Restlessness is controlled by sodium phenobarbital or paraldehyde but only if careful nursing does not quiet the patient and permit him to sleep for a few hours at a time

Once the patient has regained consciousness the danger of suffocation aspiration pneumonia bronchopneumonia thrombophlebitis and pulmonary embolism has usually passed and therapy can proceed along the lines indicated for the first group

It is often stated that death from head injury during the first 12 to 24 hr is the direct effect of primary brain injury and cannot be prevented The advisability of any surgical *procedure during this* period is much debated If the patient survives for one two or more days and remains in coma the control of brain swelling and hemorrhage by surgical means must be considered Should the condition *of the patient then begin to deteriorate* (pulse rising temperature subnormal or rising state of consciousness worsening hemiplegia more obvious plantar reflexes more clearly extensor) a decision must be made concerning an epidural or subdural hemorrhage and of increasing brain edema with temporal lobe herniation Rowbotham who has had a large experience with cases of this type recommends a right sided temporal decompression and two inspection burr holes in the left one at the Sylvian point and one at the parietal eminence for some of these patients In his opinion the indications for surgery are (1) retrogression following a period of improvement which cannot be controlled by lumbar puncture and oral and rectal hypertonic solutions or intravenous dehydration *measures (2) decerebrate* rigidity which has its onset after an interval of 24 hr (early decerebrate rigidity implies primary brain stem injury) if meningitis is ruled out (3) a dilated fixed pupil on one side with no improvement after 12 hr (4) prolonged unconsciousness associated with a persistently *high cerebrospinal fluid pressure* Not all neurologists and neurosurgeons are agreed on the value of surgical decompression but certainly the removal of a large epidural or subdural hemorrhage which cannot be diagnosed easily in the comatose patient may be a lifesaving procedure

The treatment of the patient with protracted coma is too complex to be outlined in detail here. The reader should refer to p 1770 Every patient presents special problems which must be dealt with as intelligently as possible

Patients Who Temporarily Recovered Consciousness (Lucid Interval) and Then Became Stuporous or Comatose The treatment is that of epidural *subdural and delayed cerebral hemorrhage* This has already been discussed

General Convalescence

A head injury carries dire import to most lay individuals who often fear for their mind and are concerned about their capacity to resume their place in society In former times therapeutic measures often involved *long discussions of the serious*ness of the injury protracted bed rest and inactivity all of which served only to engender greater anxiety Even worse these measures were not of proved value It is now widely acknowledged that the patient does better if his physician tends to

extensor spasms with sweating and micturition all occur after stimulation of the skin viz the *mass reflex* This stage of reflex activity may last for years unless sepsis intervenes in which case the state of spinal shock may return

Less complete lesions of the spinal cord may result in little or no spinal shock or extensor spasm incomplete voluntary motor paralysis a flaccid atrophic paralysis variable sensory impairment in the arms and a spastic weakness of the legs and a partial or complete Brown Sequard syndrome are some of the resulting clinical pictures

The final result may be permanent and complete disability rarely consistent with survival for more than a short time (days to weeks) or a gradual improvement and complete or almost complete recovery may occur Any residual symptoms after 6 months are likely to be more or less permanent

The level of the cord lesion can be determined by the clinical picture A complete paralysis of arms and legs usually indicates a dislocation at the fourth to fifth cervical If legs are paralyzed and arms can be abducted and flexed the dislocation is likely to be at the fifth to sixth cervical Paralysis only of hands and of legs indicates the level of vertebral disorder to be the sixth to seventh cervical When the motor paralysis involves muscles above the knees and sensory loss includes the twelfth thoracic dermatome the site is the eleventh to twelfth thoracics If the paralysis is below the knees and the first lumbar escapes the lesion is at the twelfth thoracic first lumbar vertebrae Prognosis for the latter preponderately a cauda equina lesion is better than for the former

Treatment

In general the treatment of spinal cord injuries is conservative and symptomatic When there is x ray evidence of bony displacement or of bone fragments pressing on the cord or when spinal subarachnoid block is present the cord should be decompressed by laminectomy This should not be undertaken however until the patient has recovered from shock If the spinal cord injury is associated with dislocation of the vertebrae traction on the neck is necessary to secure proper realignment This is accomplished by a head halter attached through the head of the bed over a pulley to a weight of 10 to 15 lb There are other more complicated techniques such as tongs which fasten onto the skull (Crutchfield) In thoracic crush injuries hyperextension can be maintained by placing a narrow pillow under the affected area Traction should be continued for 4 to 6 weeks and then a brace may be substituted The aftercare of patients with paraplegia and disturbance of vesical or rectal function is similar to that of patients with like symptoms from other causes (see Chap 272) Tidal drainage is a valuable adjunct in preventing infection stone formation and contracture and in securing return of function Daily enemas are usually the most effective means of controlling fecal incontinence Physiotherapy muscle reeducation and the application of proper braces are all important in the rehabilitation of the patient

INJURIES TO SPINAL ROOTS PLEXUSES AND PERIPHERAL NERVES

Discussions of these subjects will be found in Chaps 253 and 260

In conclusion it may be said that head and spine injuries should invite the attention of general physicians internists and neurologists There are many important lessons to be learned about the function of the human nervous system from following these cases Their treatment except in a minority of cases where there is laceration of scalp depressed fracture epidural and subdural hemorrhage or compression of the spinal cord must be conducted largely along medical lines

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Another mechanism of spinal injury occurring most often in military life is that in which missiles of high velocity pass through the vertebral canal and destroy the spinal cord In some cases they may strike the vertebral column without entering the spinal canal and agitate it so violently that the cord suffers injury The term given the temporary spinal paralysis which results is *spinal concussion* This condition may also be produced by violent falls flat on the back

A study of 2 006 cases collected from the literature by Jefferson shows that most vertebral injuries occur at the first to second cervicals fourth to sixth cervicals and eleventh thoracic to second lumbar vertebrae Industrial accidents most often involved the dorsolumbar vertebrae and those caused by falling either in a sitting position or with head down as in diving accidents affect the cervical region In the authors neuropathologic material which contains 26 cases the usual circumstances of spinal injury were a state of alcoholic intoxication and a fall down a flight of stairs auto accidents crushing industrial accidents gunshot or stab wounds and birth injury in that order of frequency The majority of these fatal cases were fracture dislocations or dislocations of the cervical spine

Mechanism of Spinal Cord Injury

The spinal cord may escape injury even though there is vertebral dislocation especially in regions where the spinal canal is large i e in the cervical and lumbar regions Or the spinal cord may be damaged without radiologic evidence of fracture or dislocation One cannot easily determine the full extent of spinal injury however even at autopsy because of difficulty in examining the vertebrae By far the most satisfactory technique for demonstrating the degree of spine injury and the presence of a tearing of ligaments with dislocation is the x ray taken laterally with the neck flexed and extended The most frequently established mechanism is a vertebral dislocation with or without fracture The upper vertebrae are displaced anteriorly and there is a break in posterior longitudinal ligament and intervertebral disk Or a sudden extension of the neck the so called whip lash injury may occur The spinal cord is most often subjected to a shearing force between the pedicles of the vertebra above and the body and laminae of the vertebra below the dislocation or is sharply angulated in violent extension of the neck Agitation of the spine as when it is struck in some part by a bullet has been postulated as a means of spinal concussion This has led to much confusion because the term is not employed here in the usual sense of a transient interruption of neural function by trauma without perceptible structural change

Pathology of Spinal Cord Injury

As a result of squeezing or shearing of the cord there are necrosis of fiber tracts and gray matter and a variable amount of hemorrhage chiefly in the more vascular gray matter These changes are maximum at the point of injury and one or two segments above and below it Rarely is the cord cut in two and seldom is the pia arachnoid lacerated This condition is best designated as *traumatic necrosis of the spinal cord* Separation of such pathologic entities as hematomyelia concussion contusion and hematorrhachis is rarely of value either clinically or pathologically As with most lesions the total disease picture is compounded of an irreversible structural lesion and a disorder of function each of which may vary in degree The extent and permanence of the clinical manifestations are determined by the relative amounts of these two An exception to this statement might be made for gunshot wounds of vertebrae Here the explosive force of the missile may shatter myelinated fibers without dislocation of vertebrae

Clinical Effects of Spinal Cord Damage

The description of traumatic paraplegia by Riddock cannot be excelled He divides the clinical picture into two stages as follows

Muscular Flaccidity or Spinal Shock The loss of function which is inflicted at the time of injury (an immediate and complete flaccid paralysis of limbs i e fourth to fifth cervical quadriplegia thoracic injury paraplegia paralysis of bladder and bowel sphincters and loss of sensibility below the level corresponding to the spinal lesion) is accompanied by a complete or almost complete suppression of reflex activity of all spinal segments below the lesion This condition is the so called "spinal shock The plantar reflexes are at first variable and may be flexor or extensor The lower extremities lose heat if left uncovered and swell if dependent Sweating is abolished Cutaneous ulcerations may develop over bony prominences Urine and feces are retained to the point where involuntary overflow or leakage results Occasionally there is priapism because of venous congestion A paralytic ileus may occur

Reflex Activity If the lumbosacral segments are undamaged spinal shock wears off in 2 to 3 weeks The first sign of this is contraction of the hamstrings with flexion or extension of the toes on plantar stimulation Then gentle and later strong involuntary flexor spasms make their appearance Ankle jerks and then knee jerks return Retention of urine and feces becomes less complete and at irregular intervals urine is expelled by active contraction of the detrusor muscle Reflex defecation and sweating also return At times flexor spasms and later ex

stance of the brain owing to some fault in embryologic development e g ectodermal cells from skin or mucous membranes which give rise to Rathke pouch cysts craniopharyngiomas and cholesteatomas or lipocytes from which the rare lipomas arise

Finally there is a group of tumors which affect the brain secondarily that is to say they arise in some other tissue and extend to the brain and rarely the spinal cord Of these there are two groups—those which reach the nervous tissues via the blood stream i e metastasize such as the carcinoma and the sarcoma and those which have their source in the epidural and osseous tissues that envelop the brain and which invade the meninges and cerebral tissues by direct extension e g chordoma osteoblastic sarcoma lymphocytoma lymphoblastoma plasmocytoma Hodgkin s granuloma and sarcoma etc

For the student of medicine the most important facts to know are (1) that many types of tumor occur in the cranial cavity and spinal canal and that certain ones are much more frequent than others (see pp 1624 to 1636) (2) that some of these tumors such as the craniopharyngioma meningioma and Schwannoma have a disposition to grow in certain parts of the cranial cavity (3) that their growth rates vary some like the glioblastoma being highly malignant others like the meningioma being benign and (4) that there are differences in the growth behavior of these several tumors some being invasive others compressive These pathologic peculiarities are important for they have valuable clinical correlations providing the explanation of slowly or rapidly progressive clinical states excellent or poor prognosis after surgical excision etc It is for these reasons that the clinician is encouraged to learn a histologic classification and to think always in terms of particular types of intracranial and intraspinal tumors

The one place where these pathologic clinical correlations tend to fail is in the glioma group of tumors i e astrocytoma—glioblastoma multiforme etc and this is regrettable because they are so common Often these gliomas are of mixed cell type For example one part of the tumor may be a typical astrocytoma and another an oligodendrocytoma Also the degree of differentiation or its opposite the degree of anaplasia varies from one part of the tumor to another As would be expected with such heterogeneous growths a biopsy sample is often quite misleading with reference to the expected clinical behavior of the tumor For example the clinician may be led to believe that a tumor which in a biopsy is composed of astrocytes is benign whereas actually the main mass of it still in the brain is a glioblastoma or a small nodule of glioblastoma in an excised specimen may suggest a hopeless prognosis when actually the remainder of the tumor in the brain is a well differentiated astrocytoma

The classification given here is modified from that of the Spanish histologist Rio del Hortega It represents his last great contribution to medical science and is based on a meticulous study by silver impregnation methods of the cell types of nearly a hundred brain tumors

CLASSIFICATION OF INTRACRANIAL AND INTRASPINAL TUMORS

I Primary tumors of
- A Nervous parenchyma
  - 1 Blastomas of glial origin
    - *a* Glioblastomas (isomorphic heteromorphic)
    - *b* Astroblastomas
    - *c* Astrocytomas
    - *d* Ependymoma (glioepitheliomas)
    - *e* Oligodendrocytomas
  - 2 Blastomas of neuronal origin
    - *a* Neuroblastomas (some medulloblastomas)
    - *b* Neurocytomas
- *B* Meninges
  - 1 Meningioma or arachnoidal fibroblastoma (meningoexothelioma)
  - 2 Fibroblastomas
  - 3 Reticulum cell sarcomas
  - 4 Hemangioblastomas (including Lindau s cyst)
  - 5 Other e g melanocarcinomas
- *C* Hypophysis and Rathke pouch
  - 1 Chromophobe chromophil adenomas of pituitary gland
  - 2 Craniopharyngiomas etc
- *D* Developmental origin ("rest cell" tumors)
  - 1 Teratomas
  - 2 Epidermoids (cholesteatomas) and dermoids
  - 3 Lipomas
  - 4 Angiomas (vascular malformations)
- *E* Adnexal organs in the brain
  - 1 Choroidal tumors (papillomas epitheliomas adenocarcinomas)
  - 2 Pineal tumors or pinealomas (pineocytomas pineoblastomas)
- *F* Nerves
  - 1 Neurinomas
  - 2 Neurofibromas
  - 3 Plexiform neuroma

II. Secondary tumors (cranial spinal, extracranial extraspinal)
- A Those arising outside the central nervous system and metastasizing via blood stream
  - 1 Carcinoma (most frequent lung breast, kidney colon infrequent stomach bile ducts liver thyroid testicle ovary uterus hardly ever metastasize to the brain prostate esophagus pancreas skin mucous membranes)
  - 2 Sarcoma (rhabdomyosarcoma osteogenic sarcoma leiomyosarcoma fibrosarcoma)
- *B* Those arising in cranial bones and enclosed para

256 TUMORS OF THE BRAIN AND SPINAL CORD

Henry de F Webster and Raymond D Adams

Tumors of the central nervous system play a very important part in neurologic medicine and occupy a distinct field by themselves It may be said of them generally that they occur in great variety are dangerous (malignant) because of size location and invasive qualities usually destroy the tissues in which they are situated and displace those around them are a frequent cause of increased intracranial pressure and are often lethal

During the first half of the twentieth century a great deal was learned about the gross and microscopic features of these tumors Also a number of classifications were introduced the most notable being those of Bailey and Cushing Hortega and Kernohan However little has been found out about their fundamental nature The experimental work done in animals in which tumors have been induced by chemical substances and the bacteriologic biochemical histologic and tissue culture studies of tumor tissue obtained from human beings during operation or post mortem have unfortunately shed little light on the fundamental problems of etiology and pathogenesis Trauma viruses chemical irritation and heredity have been suggested as causative agents but no convincing evidence on these points has been accumulated

Probably the most singular advances in this field during the present century concern diagnosis and treatment The standard textbooks of neurology written before 1900 (Osler Strumpell Oppenheim Gowers) and the monographs containing the brilliant lectures on nervous disease by Hammond Charcot Romberg Duchenne and Gowers (the reader may satisfy himself) reveal that tumor of the brain and spinal cord rarely figured in the thinking of these great clinicians Moreover it was not until 1879 that Macewen diagnosed and operated on the first intracranial tumor and shortly thereafter that Sir Victor Horsely explored the possibilities of intracranial surgery By the turn of the last century barely 50 cases had been operated upon successfully The great developments achieved within the modern era of medicine must be credited largely to Harvey Cushing and his students who showed the feasibility of removing intracranial growths and who worked out the necessary technical details of diagnosis and operative surgery Their work was aided immeasurably by the use of air to visualize the ventricular system and subarachnoid spaces [the pneumoencephalogram (PEG) and ventriculogram of Dandy] the development of arteriography (Moniz), and the invention of electrocoagulation the sucker and the Gigli saw More recently radioactive isotopes have been exploited by a number of American investigators (Moore Sweet and others) for the purpose of localizing tumor growths

CLASSIFICATION

The classification of the tumors of the nervous system like that of tumors of other viscera is primarily regional and histogenetic Subdivisions are based on the cells of origin The embryologic studies of His Cajal Hortega and their students established the existence of 14 important cell types within the cranial cavity the astrocyte oligodendrocyte microgliacyte ependymal cell choroidal epithelial cell nerve cell fibroblast specialized arachnoidal fibroblast Schwann cell histiocyte vascular endothelial cell pituitary epithelial cell pineal epithelial cell and meningeal melanophore cell Each of these basic type cells is capable of giving origin to a series of tumors which grow at various rates of speed and all gradations can usually be found between the slowest and fastest growing The tumor cells tend to differentiate as do the cells from which they arise If the growth rate is slow differentiation may be perfect just as it is in normal tissues and there is no difficulty in determining the type If the growth rate is rapid the differentiation is less complete or entirely lacking and recognition of the type cell in microscopic sections may be nearly impossible

In the first part of the classification given below the tumors are arranged in order of frequency and their terms are formed by affixing oma to the name of the cell of origin viz astrocytoma oligodendrocytoma microglioblastoma neurocytoma fibroblastoma histiocytic sarcoma etc However if the tumor cell is poorly differentiated it has become the accepted practice to denominate the tumor by the name of the embryologic precursor of that cell A poorly differentiated astrocytoma thus is called a glioblastoma an oligodendrocytoma becomes an oligodendroblastoma a neurocytoma is referred to as a neuroblastoma Special terms have had to be introduced to denote tumors whose cell of origin is uncertain but has resemblance to some particular embryologic element e g the medulloblastoma is used to designate the small cell tumor of the cerebellum in children believed to be derived from the indifferent cells of Schaper In general as with all tumors the less the degree of differentiation the greater the malignancy

In addition to the tumors derived from these 14 type cells others originate from cells ordinarily not part of the nervous system They may arise from cell rests" that are left in the meninges or sub

spaces Soon however the limits of these adjustments are surpassed and the pressure throughout the ventricles and in all parts of the subarachnoid space rises Presumably the veins in the cerebral tissues adjacent to the tumor are compressed with resulting increase in capillary pressure locally—the conditions necessary for *regional swelling* or *edema* In as much as any general increase in the cerebrospinal fluid pressure is immediately transmitted to thin walled veins the pressure in the subarachnoid space and veins is nearly the same at all times If the rise in cerebrospinal fluid pressure is slow the stasis of blood resulting from this elevated venous pressure can be compensated for by vasodilatation of arteries and arterioles and cerebral circulation is unimpaired If the rise is rapid and to high levels approaching diastolic blood pressure the blood pressure must rise usually the systolic more than the diastolic in order to maintain cerebral blood flow As a rule this is accompanied by a slow bounding pulse Under these conditions the velocity of cerebral blood flow again approaches normal Presumably these circulatory reflexes which result in the rise of blood pressure and bradycardia are initiated by venous stasis and accumulation of carbon dioxide in the vasomotor center in the medulla oblongata The respiratory centers also become affected for increases in intracranial pressure usually cause an irregularity and finally a cessation of respiration

These changes in blood pressure pulse and respiration which were studied by Kocher and by Cushing in 1901 are of the greatest importance in the clinic for they may afford valuable clues as to the existence of increased intracranial pressure Not less valuable is the papilledema or "choked disk" that can be seen with an ophthalmoscope in the optic fundi of most patients who have elevated intracranial pressure of more than a few days standing The papilledema is best accounted for by the high pressure in the subarachnoid space surrounding the optic nerves The veins that drain the retina as they course back along the optic nerves en route to the cavernous sinuses are blocked creating a lymphedema of the nerve head

Raised intracranial pressure due to a mass or enlargement of the ventricles (blockage of cerebrospinal fluid circulation) when severe causes obtundation of cerebral function This is manifested clinically by a number of characteristic symptoms (see p 296) and electroencephalographically by diffuse slowing of the electrical activity of the cortex

Another extremely important anatomic fact is that the closed cranial "box" is subdivided into fairly rigid compartments by two infoldings of dura mater one the falx which lies between the two cerebral hemispheres and the other the tentorium which separates the cerebellum from the occipital lobes These anatomic arrangements and the opening at the base of the skull through which the spinal cord and medulla are joined leave three important apertures the foramen magnum the tentorial opening or notch" and the subfalcial or supracallosal space A tumor growth in one compartment say the right middle cranial fossa, raises the pressure in that compartment more than in the others and either brain or tumor tissue tends to be displaced along lines of least resistance i e through the subfalcial space to the left half of the cranial cavity and through the tentorial opening into the posterior fossa on the right side These brain displacements are exceedingly dangerous and contribute as a rule to the death of the patient in most cases of intracranial tumor abscess trauma and subdural and epidural hemorrhage The temporal lobe–tentorial hernia is said to stretch the ipsilateral oculomotor nerve (Hutchinson s pupil—a dilated pupil on the side of a lesion and also a drooping eyelid) to displace and compress the midbrain with resulting stupor or coma bilateral pyramidal signs (often greater on the side of the hernia) decerebrate postures of extension of all four extremities and perhaps irregularity and final arrest of respiration and to distort and partially block the aqueduct of Sylvius and to narrow the perimesencephalic subarachnoid space with hydrocephalus and rising intracranial pressure Also the posterior cerebral arteries may be occluded on one side or both sides with infarction of the occipital lobes The cerebellar–foramen magnum pressure cone (herniation of cerebellar tonsils) in which the cerebellar tissue or tumor mass is displaced into the cervical spinal canal with compression of the medulla oblongata results in tilting or altered posture of the head dilated pupils impairment of consciousness and death due to respiratory arrest The physiologic and clinical effects of subfalcial herniation are not known

Herniation of the floor of the third ventricle and adjacent parts of the brain into the sella turcica may if acute be accompanied by marked reduction in vision and if chronic cause enlargement of the sella and atrophy of the pituitary gland

A knowledge of these effects of elevated intracranial pressure and of the herniations and displacements of tissue is necessary if one is to understand the clinical behavior of intracranial growths Symptoms and signs of brain tumor depend not on the invasion and destruction of important nervous structures alone but also on the pressure phenomena

Clinical and Pathologic Characteristics

As was pointed out by Bailey the intracranial tumors are far too heterogeneous to be treated as a whole The origin structure symptoms and

nasal sinuses vertebral bodies and epidural tissues

1. Carcinoma of paranasal sinuses
2. Transitional cell epitheliomas from tissue of pharynx
3. Metastatic carcinomas which metastasize to bone (prostate breast thyroid etc)
4. Multiple myeloma and plasmacytoma and other lymphomas including Hodgkin s disease
5. Chloroma
6. Chordoma
7. Osteogenic and fibrosarcoma of bone

Implicit in the histogenetic theory is the notion first advanced by Cohnheim—that the type cell from which the tumor originates is a primitive undifferentiated element that has resided within the nervous system since the earliest embryonal period. This is a likely explanation of certain teratomas dermoids hamartomas and other tumors apparently derived from cell rests but there is no evidence that this hypothesis is applicable to the gliomas and meningiomas. Indeed the careful studies of experimental tumors suggest that under certain conditions normal appearing well differentiated glial cells may be induced to undergo neoplastic metamorphosis. And the more malignant forms of tumor appear to be due to anaplasia and not to failure of differentiation. These facts can also be established when a succession of biopsies of any one tumor is arranged in a series according to cell type (cf Kernohan) and in the study of the histopathology of tumors by whole brain sections which show the relation of the differentiated to the nondifferentiated parts (Scherer)

Table 132 INCIDENCE OF INTRACRANIAL AND INTRASPINAL TUMORS AT BOSTON CITY HOSPITAL 1900 1930

Total autopsies				10 92
Total number of tumors				1 [illegible] 8
Tumors of other organs			1 [illegible] 0	
Intracranial and intraspinal tumors			188 (1[illegible].7%)	
Gliomas		81 (43.1%)		
Pituitary adenomas		6 (3 [illegible]%)		
Sheath tumors		2 (11 [illegible])		
Meningioma	18			
Acoustic neuroma	4			
Metastatic tumors		29 (15.4%)		
Blood vessel tumors		6 (3.0%)		
Congenital tumors		8 (4.3%)		
Granulomas		19 (10.1%)		
Spinal cord tumors		4 ([illegible] 1%)		
Unclassified		13 (7.1%)		

INCIDENCE

Most of the available statistics on tumors of the central nervous system have been collected in special neurosurgical clinics and are somewhat misleading for they fail to reveal their natural incidence in an unselected population. The following figures compiled by Peer are therefore rather exceptional for they avoid this error of selection and represent the natural incidence of these tumors in post mortem material during the period 1900–1930 at a time when very little neurosurgery was being performed in the hospital from which they were taken (Boston City Hospital)

These data reveal that the central nervous system and its enveloping tissues are fruitful soil for tumor growth and further that the bulk of these tumors are gliomas metastatic tumors and meningiomas. The increasing rarity of gummas and tuberculomas noted in all pathologic material during the past two decades leads the authors to believe that far less than 10 per cent of these growths are now of granulomatous nature and the rising age of the population and the increasing frequency of all types of tumors would probably raise the figure for secondary tumors. Of the gliomas approximately half are glioblastoma multiforme and the remainder are divided between astrocytoma oligodendroglioma ependymoma medulloblastoma and undiagnosed gliomas. All statistics show the peak age incidence to be the fifth decade of life with a fairly symmetric curve which reflects the lessening incidence at the extremes of age—infancy and the senescent period. In children tumors of the posterior fossa (medulloblastomas ependymomas and gliomas) predominate in adults supratentorial tumors (glioblastomas meningiomas and metastatic carcinomas) are more frequent. Males appear to be more susceptible to intrinsic tumors of the brain (gliomas) than females the ratio being 2 1. The meningioma occurs more frequently in the elderly female

INTRACRANIAL TUMORS

Pathophysiology

The cranium according to the Monro Kellie law contains three elements—nervous tissue blood and cerebrospinal fluid the total bulk of which must always be constant. Any increase in the volume of the brain for example can take place only at the expense of one of the other elements and a diminished volume of brain is compensated by an increase in the amount of cerebrospinal fluid. The cerebrospinal fluid pressure while reflecting the volume of the intracranial mass is largely maintained by the pressure under which the blood is delivered to the skull. In profound shock the cerebrospinal fluid pressure falls and at death it is zero

When a tumor or other space occupying mass forms in the cranial cavity the volume of cerebrospinal fluid within the subarachnoid and ventricular spaces is reduced and the cerebrospinal fluid is displaced into the spinal and perioptic subarachnoid

sive vascular headaches etc may also begin early in the morning on first awakening The patient does not always complain of the pain even when it is present and often he betrays its existence by placing his hand on his forehead and looking distressed

The mechanism of the headache is not known In the majority of instances the intracranial pressure is normal during the first weeks when the headache is present and one can only attribute it to distortion or alteration of blood vessels in or around the tumor Later the headache appears to be related to rises in intracranial pressure The location of the headache bears some relation to the situation of the growth Tumors above the tentorium cause headache on the side of and in the vicinity of the tumor usually in the orbital frontal temporal or parietal regions Tumors in the posterior fossa usually cause ipsilateral retroauricular or occipital headache With elevated intracranial pressure bifrontal and bioccipital headache is the rule regardless of the location of the tumor

Vomiting appears in about one third of the patients with tumor syndromes of this type and usually accompanies the headache It is more frequent with tumors of the posterior fossa Some patients may vomit unexpectedly and forcibly without preceding nausea (projectile vomiting) but others suffer both nausea and great pain Usually the vomiting is not related to the ingestion of food often occurring before breakfast

No less frequent is the complaint of *giddiness* or *dizziness* As a rule it is not described with accuracy and consists of a more or less confused sensation in the head coupled with feelings of strangeness and insecurity when its position is altered As such it can be assigned little or no localizing value Its relationship to labyrinthine stasis or "choked ear" is difficult to verify The labyrinthine function in such cases is usually normal True rotational vertigo may also occur and usually signifies disease of the eighth nerve medulla or cerebellum

One or more generalized *convulsions* is the other major symptom which calls attention to the existence of cerebral tumor Their frequency in various statistical analyses is 20 to 50 per cent of all patients with cerebral tumors The onset of a seizure during adult years and the existence of a localizing aura are always suggestive of tumor The localizing significance of seizure patterns has already been discussed (see Chap 35) The seizures may occur once or many times and may precede other symptoms for as long as 10 or more years (in cases of astrocytoma or meningioma) The manner in which a cerebral tumor can cause a seizure is not known The majority of the tumors involve the cerebral cortex though a few cerebellar tumors will be accompanied in the late stages by a generalized seizure for a reason that usually cannot be determined

The management of patients who present any one of the afore mentioned symptoms requires brief discussion The physician is well advised whenever he encounters any clinical problem of this type to consider the possibility of a cerebral tumor in its early stages A careful inquiry should then be made concerning the rest of the symptoms of this complex In other words if either a recurrent headache of a type which the patient recognizes as different from his customary headaches or a seizure appearing for the first time has occurred there is indication for a careful review of the patient s general behavior In obtaining further data one must rely heavily on the observations of other members of the family A thorough neurologic examination with careful inspection of optic fundi a test of visual fields motor reflex, and sensory functions in the limbs alertness memory facility in language (speaking reading writing and understanding the spoken word) calculation tests of visuospatial orientation (see Chap 36) must follow Sooner or later other regional or localizing symptoms and signs will be discovered and it is only by repeated examinations that one will note the earliest stages of a hemiparesis aphasia visual field defect hemianesthesia etc (For the interpretation of these localizing symptoms and signs the reader is referred to Chaps 25 35 and 36) Unmistakable signs of increased intracranial pressure may become manifest and establish the diagnosis of tumor with reasonable certainty (see Astrocytoma below)

The necessity of performing confirmatory diagnostic tests will be realized sooner or later and the decision as to the appropriate time for doing them requires balanced clinical judgment Since many of the symptoms described above are in no way specific one should rely on repeated and thorough examinations and should not proceed too quickly to expensive and difficult diagnostic tests Watchful waiting without unduly alarming the patient is the best plan for a certain period As more of the clinical picture unfolds however there comes a time when x rays of the skull and chest (always done to help rule out metastatic carcinoma) lumbar puncture (for pressure cells protein and Wassermann) and localizing electroencephalogram should be made preferably by admitting the patient to a hospital Perimetry audiograms vestibular tests and psychometric tests are also helpful in the study of many of these patients Pneumoencephalography and carotid arteriography are reserved in most medical neurologic clinics for those in whom the total clinical syndrome is already strongly suggestive of tumor These procedures are too costly and hazardous to be used routinely in every tumor suspect

treatment of each pathologic entity must be considered separately This can be done in either of two ways—by taking up seriatim each of the special types of tumor i e following a scheme based on pathology with the clinical manifestations of each tumor type being added or by making a purely clinical approach presenting the common syndromes created by intracranial tumors and then offering only a few relevant points with respect to pathology The latter scheme is followed here

It may be said at the very outset that tumors of the brain may exist with hardly any symptoms Often only a slight deficiency in mental power a slowness in comprehension or a loss of capacity in sustaining continuous mental activity suggests any deviation from normal health Specific signs that would lead to a suspicion of any real cerebral disease may be wholly wanting In some patients on the other hand there is evidence of cerebral disease in the form of a seizure or some other symptom but the evidence is not clear enough to warrant the diagnosis of a cerebral tumor In a third group the existence of a new growth in the brain may be determined with much probability by the presence of signs of elevated intracranial pressure but there are no symptoms which warrant localization of the growth Lastly the symptoms may be so clear and definite as to make it probable not only that there is a new growth within the cranium but that it is located in one particular region In fact these localized growths may create unique tumor syndromes unlike those of any other disease

These are the plain facts of clinical observation in the further exposition of this subject therefore all intracranial tumors are considered in relation to the common clinical circumstances in which they are likely to be encountered as follows

1 The patient whose presenting symptom is either a decline in general mental ability or a seizure

2 The patient with unmistakable evidence of raised intracranial pressure

3 Specific intracranial tumor syndromes

The Patient with General Symptoms of Cerebral Disease or a Seizure as His Main Complaint In general practice or on the wards of the hospital these are the patients who give the most trouble in diagnosis and about whom decisions are often made with a great degree of uncertainty Their symptoms are general as a rule and not until some time has elapsed will signs of focal brain disease be added and when they do they are not always of accurate localizing value Altered psychic functions headache giddiness and seizures comprise the usual symptomatology in this group of patients

As pointed out by Knapp some *change in mental function* may be found in nearly every patient of this type but it may be necessary to obtain observations of a person who knows the patient intimately to learn of it A lack of power of persistent application to the tasks of the day an undue irritability emotional lability a peculiar inertia " faulty insight forgetfulness inability to retain impressions indifference to social practices lack of initiative and spontaneity all of which may pass for worry anxiety or depression are the usual symptoms Much of this behavior is accepted by the patient with forebearance and if he has any complaint it is of being weak tired dizzy (nonrotational) or queer in the head Inordinate drowsiness a remarkable equanimity and stoicism may be prominent findings These symptoms become more persistent and obtrusive with the passage of time Usually within a few weeks or months the drowsiness and mental dullness increase This curious inertia and lack of spontaneity then become even more conspicuous and are evident during the interview The patient seems strangely indifferent to the questions of the examiner A long pause precedes each reply and at times the patient may not bother to respond at all Or at the very moment when the examiner has decided that the patient has not heard the question and prepares to repeat it an appropriate sensible answer is given usually in relatively few words The responses are usually much more intelligent than would be expected from the torpid mental state There are in addition patients who are confused or demented (see Chap 36) The dullness and somnolence may gradually increase and finally end in coma

Mental symptoms of this type cannot be ascribed to disease in any particular part of the brain Wilson has expressed the opinion that tumors are most likely to be accompanied by intellectual disturbance when they interfere with large association fiber systems such as the corpus callosum inferior and superior longitudinal fasciculi etc he states that cortical growths are less likely to affect the mind The drowsiness torpor inertia lack of spontaneity and general restriction of the mental horizon are usually related to increased intracranial pressure and are unrelated to the site and nature of the lesion

The *headaches* in the tumor patient may vary exceedingly In some the pain is slight temporary and dull in character in others it may be severe and unendurable being either dull or sharp but as a rule transitory or intermittent If there are any characteristics of the headache they are its nocturnal occurrence its presence on first awakening and its deep nonpulsatile quality However these are not specific attributes since migraine hyperten

malignant degeneration and present as mixed astrocytomas and glioblastomas In 94 gliomas studied post mortem by Scherer of which 18 were astrocytomas all but 5 showed areas of glioblastoma multiforme This fact as well as the frequent finding of fiber forming astrocytes throughout the tumor (obviously tumor cells and not reacting astrocytes) has led Kernohan and his associates to conclude that the glioblastoma astroblastoma and astrocytoma are all derived from mature astrocytes which have undergone various degrees of anaplasia Thus the glioblastoma is an astrocytoma of grade 4 malignancy and the astroblastoma is of grade 2 or grade 3 malignancy The authors observations are for the most part in agreement with this opinion though one must admit the possibility that glial tumors of other cell types upon becoming anaplastic might occasionally give rise to a glioblastoma The astroblastomas fall between the astrocytoma and glioblastoma in both clinical and pathologic characteristics

The astrocytoma may cause trivial symptoms for a long period of time Seizures headaches and bizarre mental symptoms may be present for several years in a few instances more than 10 before the diagnosis is made The average survival period after the first symptom is 67 months in cerebral growths and 89 months in cerebellar ones The cystic astrocytoma of the cerebellum is particularly benign and some patients are alive and well as long as 20 years after part of the cyst was excised Here of course accuracy of the original diagnosis of neoplasm is always open to question The astrocytoma of the pons optic nerves and chiasm will be discussed in more detail later on in this chapter

OLIGODENDROCYTOMA The oligodendrocytoma is a relatively rare cerebral tumor (5 to 10 per cent of gliomas) and is usually slow in its rate of growth (average span of evolution is 66 months) It is generally a soft solid tumor rarely cystic or hemorrhagic and through its tendency to calcify (spherules and particles of calcium in microscopic sections) often casts a shadow in the roentgenogram of the skull Microscopically it is composed of small round cells with spherical nuclei and cytoplasm that stains poorly forming a halo around the nucleus Seizures are uncommon and generalized or focal cerebral symptoms may be present for a long time before the mass of the tumor declares its presence by increased intracranial pressure

EPENDYMOMA AND EPENDYMOBLASTOMA Although occasionally this tumor presents as a solitary mass in a cerebral hemisphere in adults presumably arising from the ependymal wall of the lateral ventricle its most distinctive form is a papillary growth filling the fourth ventricle of children It will be discussed further on p 1632

MENINGIOMA (ARACHNOIDAL FIBROBLASTOMA AND ENDOTHELIOMA) This is a benign tumor composed of specialized arachnoidal lining cells arising usually in places where there are arachnoidal villi Since these clusters of arachnoidal cells penetrate the dura in the vicinity of the venous sinuses they often appear to originate from the dura itself hence the old term "dural endothelioma Grossly the tumors are firm gray white lobulated bulbous or plaquelike masses which indent or compress but do not invade brain tissue Many of them are highly vascular In size they are variable some are only a centimeter or two in size and are turned up as incidental findings at autopsy Others usually those which have produced symptoms have attained a size of 3 to 4 cm or more The cellular composition permits easy identification The cells are of uniform type and have the peculiar disposition to encircle one another and to form characteristic whorls and psammoma bodies The common sites of these tumors are the olfactory groove tuberculum sellae parasagittal region Sylvian fissure cerebellopontine angle and spinal canal In as much as they lie on the surface of the brain in or next to the dura changes in the skull are frequent The skull may be eroded over the tumor and the diploic vessels which provide part of the blood supply of the tumor dilate and are unusually prominent in an x ray Or the tumor cells may invade the bone and stimulate osteoblastic activity as a consequence of which a bony bulge may be seen and felt or an endostosis is visualized on the inner table of the skull in an x ray The meningioma must be listed with metastatic carcinoma and the true cholesteatoma as the three tumors most likely to cause a visible cranial boss in relation to cerebral symptoms (*benign exostoses are neurologically asymptomatic*) Offering a broad vascular meningeal surface as they do these tumors often elevate the protein of the cerebrospinal fluid Their striking vascularity accounts for the characteristic blush seen in arteriograms and the excessive permeability of the vessels as well as the superficial location of the tumors make them ideal subjects for localization with radioactive isotopes The displacement without invasion of cerebral tissue probably explains the interruption locally of normal alpha frequencies in the EEG with sharp waves or theta waves in contrast to the delta waves so often found in infiltrative gliomas Multiple meningiomas may be found particularly in cases of neurofibromatosis

These tumors may be found at any age but are more frequent in advanced years especially in women Their slow growth is reflected in the long duration of symptoms in many cases and their indentation of cerebral cortex explains the high incidence of focal convulsions Aside from the general cerebral disorder and seizures those tumors

One proceeds on the basic assumptions that tumor symptoms and signs are progressive and that the treatment of tumors of the brain may proceed satisfactorily from the point at which diagnosis becomes fairly obvious from the clinical facts alone Experience teaches that little gain comes from attempting early diagnosis and early operation before signs are well established This point will be further discussed under Treatment

Tumors Which Tend to Produce General Cerebral Symptoms or Seizures The following tumors are most likely to produce initial convulsions or a vague syndrome of headache giddiness vomiting dull or stuporous state and psychic changes glioblastoma multiforme astrocytoma oligodendroglioma metastatic carcinoma meningioma and primary reticulum cell sarcoma of the cerebrum

GLIOBLASTOMA MULTIFORME In all statistic analyses of surgical and post mortem material glioblastoma multiforme is responsible for more than 25 per cent of intracranial gliomas and for more than 90 per cent of gliomas of the cerebral hemispheres in adults Approximately 20 to 30 per cent of the cerebral tumors are bilateral occupy more than one lobe of a hemisphere or show multicentric foci of growth Although predominantly cerebral in location similar tumors may be observed in the brain stem cerebellum or spinal cord The peak incidence is in middle adult life but no age group is spared

The glioblastoma is a highly malignant tumor which infiltrates the brain extensively and may attain enormous size It may extend to the meningeal surface or the ventricular wall which probably accounts for the elevation of protein (often over 100 mg per cent) in many cases and sometimes a pleocytosis of 10 to 100 or more cells mostly lymphocytes The tumor has a variegated appearance being a mottled gray red orange or brown depending on the degree of necrosis and whether hemorrhage is recent or old It is highly vascular and in an arteriogram one can often see a network of abnormal vessels mistaken at times for a hemangioma and the displacement of normal vessels which may result from any mass lesion Some part of one lateral ventricle is often distorted and both lateral and third ventricles are displaced contralaterally which may be demonstrated by pneumoencephalography or ventriculography The vessels in the tumor are excessively permeable to fluorescein P^{32} radioactive arsenic etc which is the basis for radioactive scanning techniques Calcification and cavity formation are not prominent The characteristic microscopic pathologic findings are great cellularity with pleomorphism of cells and hyperchromatism of nuclei identifiable astrocytes with fibrils in combination with astroblasts tumor giant cells and cells in mitosis a curious neoplastic proliferation of the cells of small vessels (adventitial and endothelial) necrosis pseudopalisading of viable cells hemorrhage and thrombosis of vessels Temporal lobe–tentorial herniation midbrain compression midbrain and pontine hemorrhages and increased intracranial pressure are usually the immediate causes of death At autopsy the tumor is often seen spreading along cerebrospinal fluid pathways (seedings around spinal cord and cauda equina) but metastasis outside the craniovertebral cavity is almost unheard of except postoperatively when dura scalp and draining cervical nodes are invaded

Clinically the diffuse cerebral symptoms and seizures (present in 30 to 40 per cent of cases) usually give way to a more definite frontal temporal parietooccipital or callosal syndrome in a few weeks or months Seldom however do the symptoms and signs point to one lobe and often one is satisfied to be able to specify the region of the hemisphere which is involved When the corpus callosum is invaded as it so often is the so called callosal syndrome (apathy drowsiness forgetfulness apractic and agnostic disturbance) may precede or follow other lateralizing signs Increased intracranial pressure usually follows the other neurologic signs There are no other important clinical abnormalities The sedimentation rate white cell count and hemoglobin remain normal Survival for more than a few months or a year after operation is exceptional and should lead one to question the accuracy of histologic diagnosis

ASTROCYTOMA The astrocytoma may occur anywhere in the brain or spinal cord Favored sites are cerebrum cerebellum thalamus optic chiasm and pons It is a slowly growing tumor of infiltrative character with a marked tendency to undergo some type of degeneration with the formation of large cavities or cysts In some instances much of the tumor may be composed of a cyst surrounded by a thin border of astrocytic tissue and the only sizable mass of tumor tissue may be a mural nodule Others of these tumors are noncystic grayish white firm and relatively avascular almost indistinguishable from normal white matter with which they may merge imperceptibly Calcium deposits may occur in parts of the tumor and may be seen in a plain x ray of the skull The cerebrospinal fluid is acellular the only abnormality being the increased pressure and elevated protein in some cases The tumor by its mass may distort the lateral and third ventricles (seen in pneumoencephalogram or ventriculogram) and may be seen to displace the anterior and middle cerebral arteries in a carotid arteriogram Microscopically the tumor tissue is composed of well-differentiated astrocytes of fibrillary protoplasmic or transitional type

The majority of cerebral astrocytomas undergo

upon awakening vomiting that may or may not be unexpected and projectile mental torpor and papilledema (see Chap 31)] when first seen The physician confronted with this clinical problem is forced to take immediate action for the condition is potentially dangerous A critical rise in intracranial hypertension may occur at any time and result in coma respiratory arrest and death Admission to a hospital with a neurosurgical service is therefore usually urgent Nevertheless all the medical aspects of the patient s problem should first be worked out

Three questions demand immediate answers (1) Does the patient have a space occupying intracranial lesion? (2) Where in the cranial cavity is it situated? (3) What is its nature? With respect to the first question it is well to keep in mind that a number of medical conditions may simulate an intracranial growth that causes only the general symptoms of increased intracranial pressure These are (1) "pseudotumor cerebri (2) hypertensive encephalopathy (3) chronic pulmonary disease with hypercapnia and hypoxia (4) chronic adhesive arachnoiditis and/or aqueductal stenosis (5) thrombosis of cerebral veins and dural sinuses (6) Addison s disease with encephalopathy or hypoparathyroidism with papilledema Several of these conditions have been discussed elsewhere in this book and it is sufficient to mention them briefly others have not been considered before and will be discussed in detail

Pseudotumor Syndromes In the condition of *pseudotumor cerebri* (meningeal hydrops) the patient more often than not a young woman complains of headaches of some weeks standing and when first examined is found to have papilledema or choked disk with slightly constricted visual fields and enlarged blind spots Other neurologic signs with the occasional exception of a vague dizziness diplopia due to a slight abducens weakness or paresthesias of some part of the body are conspicuously absent and the patient appears remarkably bright and well The cerebrospinal fluid is acellular with normal protein content and small or normal sized ventricles in a ventriculogram With daily then biweekly then weekly lumbar punctures to lower the cerebrospinal fluid pressure most of the patients gradually recover over a period of weeks to months Extremely high cerebrospinal fluid pressure with episodes of cloudy vision (obscurations) may herald the onset of blindness and require a right subtemporal decompression as an emergency measure The cause of the condition is unknown Extreme hypertension (diastolic pressures of 120 mm or over) retinal arteriolar changes with hemorrhages and exudates in the periphery of the optic fundi signs of renal disease and headache convulsions confusion stupor or coma are the basis of the diagnosis of *hypertensive encephalopathy* (see p 1600) *Chronic emphysema or other lung disease with cyanosis dyspnea cough signs of cor pulmonale with right sided congestive heart failure and secondary polycythemia* may be attended by bilateral papilledema elevated cerebrospinal fluid pressure high venous pressure severe headache drowsiness stupor or coma and a peculiar lapse in the posture of the outstretched limbs and other contracted skeletal muscles (flapping movements or asterixis similar to the flap in impending liver coma) The finding of an elevated carbon dioxide-combining power and diminished arterial oxygen concentration substantiate the diagnosis *Chronic adhesive arachnoiditis* due to chronic fibrosing meningeal diseases such as syphilis postspinal anesthesia arachnoiditis and cryptogenic meningeal diseases may be attended by headache papilledema seizures blindness paraplegia or quadriplegia The cerebrospinal fluid protein may be normal or elevated with or without a "dynamic block and the lateral and third ventricles are enlarged in the ventriculogram Syphilis and the other chronic meningitides may also cause *aqueductal stenosis* owing to a proliferative gliotic ependymitis with enlargement *of the lateral and third ventricles* (see Chap 253) *Thrombosis of the jugular veins and of the lateral and posterior parts of the superior sagittal sinus* may result in increased intracranial pressure with otherwise normal cerebrospinal fluid and small ventricles (see Chap 146) Several cases of unexplained papilledema with headache drowsiness and confusion and elevated cerebrospinal fluid pressure have been observed in conjunction with *Addison s disease* (Jefferson) and also in rare cases of hypoparathyroidism The mechanism is not known *Retrobulbar neuritis of demyelinative type* if it extends to the optic nerve head may cause a papillitis with elevation and edema of the optic disk and even hemorrhages around the disk There is invariably an early development of a marked impairment of vision and large central scotomas The prominent visual change and the absence of clinical and laboratory evidence of increased intracranial pressure distinguish this condition from true papilledema and also from pseudopapilledema (spurious papilledema) and tortuosity of retinal veins—a normal ophthalmoscopic picture in some patients especially those with marked hyperopia Severe anemia may also cause hemorrhages exudates and a *suspicion of papilledema* which may at times be confused with the retinal picture of neoplasm

False Localizing Signs" If the clinical findings permit the exclusion of the afore mentioned conditions there is reasonable certainty that the patient has an intracranial growth The problem then is to search for signs which will localize the lesion In doing this several pitfalls must be avoided One

which occupy special locations create unique syndromes Some of these will be discussed later starting on p 1634

METASTATIC CARCINOMA Of the secondary tumors of the brain only metastatic carcinoma will be discussed here because the other tumors that metastasize to the brain are decidedly rare Carcinomas reach the brain by hematogenous spread Probably 35 to 40 per cent come from the lung and approximately 15 per cent each from the breast gastrointestinal tract (usually colon or rectum) and kidney Stomach melanotic carcinoma of the skin gallbladder liver thyroid testicle uterus ovary etc account for the remainder no one of them usually being responsible for more than 3 or 4 per cent of secondary tumors of the brain Carcinoma of the prostate esophagus oropharynx or skin (except for melanocarcinoma) rarely if ever is disseminated in the brain In more than 75 per cent of cases the metastases are multiple and are scattered through both the cerebrum and cerebellum often near the surface and involving white matter cortex and meninges The hypernephroma and thyroid carcinoma have a greater tendency to form solitary metastases than other tumors and as with the chorionepithelioma and some lung tumors the metastases are likely to be hemorrhagic The tumor tissue generally has all the gross and microscopic features of any carcinomatous implant and excites rather little glial reaction but much edema

The usual clinical picture in metastatic carcinoma of the brain has already been described under Glioblastoma Multiforme A number of rather striking clinical neurologic syndromes also occur One that is particularly difficult to diagnose is a widespread *carcinomatous meningoencephalopathy* with headache nervousness depressed mood trembling mental confusion and forgetfulness the whole picture looking very much like that of general paresis Carcinomatosis of the cerebellum with headache dizziness and ataxia the ataxia being brought out only by having the patient walk is another difficult condition to diagnose during life Such patients may be regarded as hysterical until sudden death due to a cerebellar pressure cone terminates the illness Here the metastases are more or less limited to the midline structures of the cerebellum Symptoms and signs referable to one or several cranial and spinal nerve roots may be combined with headache and confusion in widespread *carcinomatosis of the craniospinal meninges* (carcinomatous meningitis) Usually the cerebrospinal fluid contains a few white blood cells (lymphocytes) and an elevated protein Tumor cells can often be identified in Papanicolaou stains of cerebrospinal fluid sediment and if many are present in the meninges the sugar values may be subnormal even as low as 0

When the syndromes due to these several varieties of metastatic tumor are fully developed diagnosis is relatively easy If only headache and vomiting are present a common error is to explain these symptoms on a psychologic basis One should make a psychiatric diagnosis only if the patient has the standard symptoms of the mental illnesses (see pp 361 362) A lumbar puncture chest x ray (positive in 75 per cent of cases of metastatic tumor of brain) and other x rays (gastrointestinal series barium enema and pyelograms if symptoms point to these organs) are advisable The metabolic neurologic syndromes which accompany carcinoma but which are not due to tumor invasion of the central nervous system (multiple neuropathy especially with carcinoma of the lung) polymyositis and spinocerebellar degeneration (ovarian and other carcinomas) should also be kept in mind

TUMORS OF INFECTIVE ORIGIN (GRANULOMAS AND PARASITIC CYSTS) Tuberculoma is much less frequent in the United States than it was 20 years ago and gumma has become almost nonexistent In fact a patient with serologic syphilis and a positive Wassermann reaction of the cerebrospinal fluid has a greater chance of having two diseases a cerebral tumor and asymptomatic neurosyphilis than a gumma The tuberculoma may occur in any part of the brain but in children it is more likely to develop in the posterior fossa i e in the cerebellum or brain stem than in the cerebrum Often there are a small number of cells and an increased protein content in the cerebrospinal fluid because the lesion frequently lies contiguous to the meninges and it may at any time give rise to a tuberculous meningitis with typical cerebrospinal fluid formula (50 to 300 cells increased protein decreased sugar and chloride content)

In South America tuberculoma and gumma are much more frequent and one can usually depend on evidence of disease in other parts of the body especially the lungs and characteristic changes in the cerebrospinal fluid (see Chap 31) to indicate the nature of the lesion In addition cysticercus cellulosae and hydatid cysts are common lesions and should always be suspected when seizures increased intracranial pressure or diffuse cerebral symptoms develop in the adult X rays of the skull and skeletal muscles (e g thigh) may reveal characteristic calcific deposits in cysticercosis Torula and other fungous granulomas and *Schistosoma japonicum* infection may also present as space occupying cerebral lesions (see pp 1134 1139 985)

Patients with Unmistakable Signs of Increased Intracranial Pressure When First Seen A certain number of patients show all the characteristic symptoms and signs of increased intracranial pressure [periodic bifrontal and bioccipital headaches which awaken the patient during the night or are present

duct of Sylvius Often it extends anteriorly into the third ventricle and may then compress the hypo thalamus Microscopically it is composed of large spherical epithelial cells (much like those of a semi noma) separated by a network of reticular con nective tissue which contains many lymphocytes The gliomas have the usual morphology of an astro cytoma of varying degrees of malignancy Children adolescents and young adults either male or fe male may be affected In some cases the clinical syndrome consists solely of symptoms and signs of increased intracranial pressure and the diagnosis can be made only by a ventriculogram which reveals the tumor The most characteristic symptom however is an inability to look upward (Parinaud s syn drome) with slightly dilated pupils which react on accommodation but not to light Sometimes ataxia of the limbs choreatic movements or spastic weak ness appears in the later stages of the illness A Torkildsen ventriculo-cisterna magna shunt of cere brospinal fluid and x ray therapy have been remark ably successful in controlling the symptoms At tempts at surgical removal of the tumor have usu ally proved fatal

COLLOID (PARAPHYSEAL) CYST OF THE THIRD VEN TRICLE This is a papillomatous structure always situated in the anterior extremity of the third ven tricle between the interventricular foramens and attached to the roof of the ventricle Usually it is about a centimeter in diameter is oval or round with a smooth external surface and is filled with a glairy colloid material The wall is composed of a layer of epithelial cells surrounded by a capsule of fibrous connective tissue These benign cysts may exist for long periods of time they produce neuro logic symptoms by blocking the third ventricle and causing an obstructive hydrocephalus This tumor should be suspected when the following clinical syndromes are found dementia with or without headache intermittent severe bifrontal bioccipital headaches sometimes modified by posture (ball valve obstruction of the third ventricle) crises of headache with obtundation bilateral paresthesias dim vision and weakness of legs with sudden falls

CRANIOPHARYNGIOMA (SUPRASELLAR OR RATHKE POUCH CYST HYPOPHYSEAL DUCT TUMORS ADAMAN TINOMAS AMELOBLASTOMAS) This is a benign con genital or rest cell tumor By the time it has grown to a diameter of 3 to 4 cm it is almost always cystic Usually it lies above the sella turcica de pressing the optic chiasm and extending up into the third ventricle Less often it is subdiaphragmatic i e within the sella where it compresses the pitui tary body erodes one part of the wall of the sella or a clinoid process but seldom balloons the sella like a pituitary adenoma. The tumor is oval round or lobulated and has a smooth surface The wall of the cyst and the solid parts of the tumor consist of cords and whorls of epithelial cells often with inter cellular bridges and keratohyalin separated by a loose network of stellate cells The cyst contains dark albuminous fluid and cholesterol crystals Cal cium deposits are found in nearly all of them and can be seen in plain x rays of the suprasellar region in about 40 per cent of cases The sella beneath the tumor tends to be flattened and enlarged This is more often a tumor of children than of adults but patients of all ages may be seen with it In chil dren adiposity delayed or infantile physical and sexual development (Froehlich s syndrome or Lorain syndrome—cf Chap 253) headaches vomit ing dim vision with chiasmal field defects (see p 269) optic atrophy or papilledema comprise the clinical picture In adults waning libido amen orrhea slight spastic weakness of the legs head ache without papilledema and mental dullness and confusion are often found Later drowsiness dia betes insipidus and disturbances of temperature regulation may occur indicating hypothalamic in volvement (see p 268)

In the differential diagnosis of these several tu mor syndromes a careful clinical analysis is often more important than laboratory procedures Arteri ography and electroencephalography are not so helpful as in cerebral tumors The one test which though somewhat hazardous is likely to give the most useful information is a ventriculogram or a combined ventriculogram pneumoencephalogram

Tumors of the Posterior Fossa and Third Ven tricle in Infancy and Early Childhood Any discus sion of tumors of the brain would be incomplete if some reference were not made to intracranial tumors of infancy and childhood for they often create clinical problems of a special type Fully two thirds of tumors before the age of puberty are medulloblastomas ependymomas cerebellar astro cytomas and pontine gliomas are situated in the posterior fossa and produce increased intracranial pressure Hence this brief digression is appropriate at this point in the general exposition

As stated in Chap 253 in the section on congenital hydrocephalus the cranial sutures do not close until about the time of puberty and an elevation of intracranial pressure especially if it occurs in the first months and years of life results in separation of sutures and enlargement of the head This is evident by inspection by head meas urement and in x rays and it is also demonstrated by finger percussion of the parietal eminence of the skull which produces a peculiar sound as though a cracked cup or bowl were being tapped (Macewen s sign) The separation of sutures by enlarging the intracranial cavity permits temporary restitution of intracranial pressure and amelioration of symptoms Papilledema does not develop if the head enlarges

common source of error is to place undue reliance on a sign which proves to have no localizing value whatsoever With experience in this field one comes to distrust any symptom or sign which develops late after headache and increased intracranial pressure have been established for it often turns out to be a "false localizing sign" Under these circumstances drowsiness slowness in response inattentiveness and emotional blunting can be found as often with cerebellar as with cerebral growths Unilateral or bilateral abducens palsy is another common false localizing sign (Collier) and reference has already been made to the drooping eyelid dilated pupil ipsilateral hemiparesis and bilateral Babinski signs and coma in temporal lobe herniation Jacksonian and generalized seizures and ipsilateral or bilateral pyramidal signs may be observed in the advanced stages of a cerebellar tumor On the other hand relatively slight focal signs that may be easily overlooked are sometimes the only clues as to the localization of the tumor Examples are ataxia of gait (but not of limbs) and head tilt in cerebellar tumors paralysis of upward gaze with the Argyll Robertson pupillary phenomenon in pinealomas pale optic disks and chiasmal field defects in craniopharyngiomas homonymous visual inattentiveness and sensory extinction (see pp 279 and 342) in posterior cerebral tumors and a facial asymmetry in emotional expression in frontal tumors

Tumors Which Tend to Produce Elevated Intracranial Pressure without Conspicuous Localizing Signs The tumors most likely to cause increased intracranial pressure with few or no focal or lateralizing signs are medulloblastoma ependymoma of the fourth ventricle hemangioblastoma pinealoma colloid cysts of the third ventricle gliomas of tegmentum of the midbrain blocking the aqueduct and craniopharyngioma In addition in many of the cerebral gliomas discussed above particularly those of the corpus callosum and frontal lobes increased intracranial pressure may precede focal cerebral signs

MEDULLOBLASTOMA This is a rapidly growing tumor which arises in the posterior part of the vermis of children The midline part of the cerebellum may be invaded and completely destroyed The tumor also fills the fourth ventricle and compresses the medulla The tonsils of the cerebellum are forced down into the cervical spinal canal (cerebellar pressure cone) in fatal cases Seedings of the tumor may be seen on the walls of the third and lateral ventricles on the meningeal surfaces of the brain and around the spinal cord The tumor is solid reddish gray in color and poorly demarcated from the adjacent brain tissue It is very cellular and the cells are small closely packed with little cytoplasm many mitoses scant stroma and a tendency to form clusters or pseudorosettes As already stated these cells resemble the indifferent cells which Schaper described in the chick embryo and are thought to be capable of differentiation into either glial cells or neuroblasts Bailey and Cushing introduced the name *medulloblastoma* in 1925 Although medulloblasts as such have not been described in the fetal or adult human brain and the cell type is not known for certain the term is retained if for no other reason than its familiarity In adults a somewhat similar neuroblastoma of less malignant character may arise in the cerebral hemisphere

The clinical picture is distinctive Typically the patient a child of five to ten years becomes listless vomits repeatedly and has a morning headache The first diagnosis which suggests itself may be gastrointestinal disease or abdominal migraine Soon however a stumbling gait frequent falls and a squint lead to a neurologic examination and the discovery of papilledema Ataxia of the limbs may be absent at all times (cf Chap 26 on the syndrome of flocculonodular lobe) Decerebrate attacks (tonic cerebellar fits) may occur in the late stages of the disease The tumor is highly radiosensitive and surgery with x ray treatment may prolong life for several years

EPENDYMOMA AND PAPILLOMA OF THE FOURTH VENTRICLE This tumor also arises from the walls of the fourth ventricle in children It is a firm whitish lobulated growth composed of small cells arranged in the form of small rosettes around vessels or central clear areas and containing blepharoplasts in their cytoplasm Mitoses are absent if present they mark the tumor as an ependymoblastoma The clinical syndrome is much like that of the medulloblastoma except for the absence of ataxia of gait The tumor is not very sensitive to x ray and surgical removal offers the only hope of survival The papilloma or papillary adenocarcinoma of the choroid plexus of the fourth ventricle gives rise to a similar syndrome

HEMANGIOBLASTOMA OF THE CEREBELLUM The disease of Lindau was described in Chap 253 Dizziness ataxia of gait or of the limbs on one side symptoms and signs of increased intracranial pressure and in some instances a retinal angioma (von Hippel's disease) and polycythemia constitute the neurologic syndrome Familial incidence is well known Craniotomy with opening of the cerebellar cyst and excision of the mural hemangioblastomatous nodule may be curative

PINEALOMA This may be either a terotoma or a glioma of the pineal gland The teratoma is a firm discrete noninvasive mass which usually reaches 3 to 4 cm in greatest diameter It compresses the superior colliculi and sometimes the superior surface of the cerebellum with narrowing of the aque

ternal auditory meatus and obliteration of the lateral recess of the fourth ventricle in a pneumoencephalogram must be depended upon for diagnosis Dementia may later be the presenting syndrome and the deaf ear may be overlooked Unilateral cerebellar ataxia and dizziness may predominate and definite signs of involvement of the fifth seventh and eighth cranial nerves may not be found The treatment is surgical excision

The *trigeminal* or *gasserian ganglion neurinoma* and *meningioma* of the *cerebellopontine angle* may be indistinguishable from an acoustic neurinoma They should always be considered if early tinnitus and deafness and an unresponsive labyrinth ("dead labyrinth") are not the initial symptoms of the cerebellopontine angle syndrome A true *cholesteatoma of the temporal bone* may simulate this clinical picture but usually the facial weakness is early and severe the ear is deaf and labyrinthine function is absent whereas the other cranial nerve signs cerebellar ataxia and increased intracranial pressure are absent The *tumor of the glomus jugulare* (a flat ovoid body found in the adventitia of the jugular bulb immediately below the floor of the middle ear and near the ramus tympanicus of the ninth cranial nerve) may like the acoustic neurofibroma basal meningioma metastatic cancer syphilitic meningitis neurofibroma of other cranial nerves and vascular malformation cause unilateral lower cranial nerve palsies (see p 291) It is a purplish red highly vascular tumor composed of large epithelioid cells in an alveolar pattern and an abundant capillary network Partial deafness facial palsy dysphagia and unilateral atrophy of the tongue combined with a vascular polyp in the auditory meatus and a palpable mass below and anterior to the mastoid eminence often with a bruit comprise the syndrome The jugular foramen is eroded (visible by x ray) and the cerebrospinal fluid protein may be elevated Women are affected more than men and the peak incidence is during middle adult life The tumor grows slowly over a period of many years sometimes 10 or more The treatment is x ray radiation

THE PITUITARY ADENOMAS These tumors which are so common particularly in late adult life often are discovered when a patient begins to complain of a visual disturbance A unilateral or bilateral temporal hemianopia progressing to blindness with optic atrophy is the usual finding and with x ray evidence of an expanded sella turcica leads to a diagnosis of pituitary adenoma As the growth enlarges and extends laterally an oculomotor palsy is occasionally seen and large suprasellar extensions may involve the hypothalamus or temporal lobe If there are signs of acromegaly one may assume that an eosinophilic adenoma is present if not and signs of pituitary insufficiency are present (amenorrhea without hot flashes" sexual impotence etc—cf Chap 62) there is usually a chromophobe adenoma Basophilic adenomas one of the causes of Cushing s syndrome rarely if ever produce enlargement of the sella or visual symptoms The diagnosis is made from the endocrine picture (see Chap 62) The cerebrospinal fluid is usually under normal pressure and protein is elevated only in exceptional cases Other tumors may rarely expand the sella (craniopharyngioma) and there are also rather wide normal variations in its size Hence the diagnosis of pituitary adenoma should not be made because of minor enlargements in the absence of neighborhood neurologic signs In doubtful cases a pneumoencephalogram permits visualization of the suprasellar extension of the tumor Treatment is x ray radiation and if vision is threatened despite x ray therapy either transnasal or transfrontal surgical excision

MENINGIOMA OF THE SELLAR TUBERCLE This tumor arises from the region of tuberculum sellae and as it grows it lifts the optic chiasm upward and backward The optic nerves become stretched and separated With further increases in size it may expand anteriorly compressing the olfactory bulbs or posteriorly compressing the hypothalamus When the tumor is small the only symptom is bitemporal hemianopia later blindness with optic atrophy anosmia mental deterioration hemiparesis uncinate seizures oculomotor palsy and amenorrhea are added The diagnosis is made when a middle aged person is found to have a bitemporal hemianopia normal sized sella and no signs of hypothalamic or pituitary involvement Saccular aneurysm of the carotid artery and rarely craniopharyngioma extrasellar pituitary adenoma and Boeck s sarcoid may be confused with it The treatment is surgical excision

MENINGIOMA OF THE SPHENOID RIDGE This tumor arises from arachnoid cap cells over the lesser wing of the sphenoidal bone As it increases in size it may expand medially to encroach on structures in the wall of the cavernous sinus anteriorly to invade the orbit or laterally to erode or invade the temporal bone Most prominent among the symptoms are a slowly developing unilateral exophthalmos slight bulging of the bone in the temporal region and roentgenologic evidence of thickening or erosion of the lesser wing of the sphenoid bone Variants of the clinical syndrome include oculomotor palsy or syndrome of Foix (cf p 291) blindness in one eye with optic atrophy anosmia (and sometimes the Kennedy syndrome—see below) mental changes uncinate fits and increased intracranial pressure Sarcomas arising from the skull bones metastatic carcinoma orbitoethmoidal osteoma tu

The cardinal symptoms of a posterior fossa tumor in an infant or small child are different from those of the adult They consist of weakness vomiting and unsteadiness of gait These symptoms may fluctuate in severity tending to subside temporarily with further separation of sutures The vomiting may be prominent and occur at any time of day Often it is not preceded by nausea An erroneous diagnosis of cyclic vomiting or vomiting due to an emotional disturbance may be made Unlike vomiting due to intraabdominal disease this vomiting is not accompanied by abdominal pain Weakness and listlessness are also present but are more difficult to interpret Headache is seldom a complaint and seizures are rare

In tumors of the vermis of the cerebellum (medulloblastoma) the ataxia of gait and disinclination to walk (see Chap 26 on the vermis syndrome) without evident incoordination of the movements of arms or legs can usually be demonstrated by careful observation In astrocytoma or hemangioblastoma of one cerebellar hemisphere the ipsilateral arm and leg are ataxic (see Chap 26 on the syndrome of neocerebellum) and a nystagmus which is much coarser on looking to the side of the lesion than to the opposite side is present Also the head is often tilted with tumor of the cerebellar hemisphere the ear on the side of the tumor being brought towards the shoulder The ipsilateral arm is hypotonic and swings less than the contralateral one in walking General hypotonia and bilateral extensor plantar reflexes are late signs and are of less value in localization

These cerebellar signs when added to the general picture described above regardless of whether or not papilledema is present point to the posterior fossa as the site of a tumor More difficult to diagnose are the patients with only signs of hydrocephalus This condition may come about with a medulloblastoma arising in the upper vermis and filling the fourth ventricle or with an ependymoma arising from either the roof or the floor of the fourth ventricle Occasionally a craniopharyngioma may cause only hydrocephalus but then a peculiar docility an appearance of maturity due to greater interest in mental than physical activities and a retardation of growth may be helpful signs in identifying a lesion within the walls of the third ventricle

In later childhood separation of sutures and head enlargement are slight and headache and papilledema are the common signs of increased intracranial pressure just as in the adult

Patients with Symptoms and Signs of a Slowly Progressive Lesion in a Particular Region of the Cranial Cavity In this condition general cerebral symptoms and the signs of increased intracranial pressure occur late or not at all The physician arrives at the correct diagnosis by being able to make an anatomic or regional diagnosis from a set of neurologic findings and by reasoning that the etiology must be neoplastic because of the slowly progressive nature of the illness Special x rays of the skull cerebrospinal fluid examination and depending on the location of the disease either pneumoencephalography or arteriography will usually confirm the clinical impression

The following tumors produce unique syndromes usually diagnostic of a special type of tumor

ACOUSTIC NEUROFIBROMA OR NEURINOMA This slowly growing benign tumor may occur as a solitary lesion or as a part of the syndrome of neurofibromatosis Grossly by the time of operation the tumor has usually attained a size of 4 to 6 cm in diameter It arises from the extramedullary part of the eighth cranial nerve usually within the internal auditory meatus where the intracranial part of the nerve first acquires the histologic character of a peripheral nerve i e with Schwann cells and fibroblasts The space in which it lies is the cerebellopontine angle i e between the cerebellum pons and medulla posteriorly the petrous pyramid anteriorly and the tentorium above The internal auditory meatus is usually enlarged (visible in x rays) the middle cerebellar peduncle and the anterolateral part of the cerebellum are depressed and the trigeminal facial glossopharyngeal and vagus nerves are displaced and stretched over the surface of the growth The fourth ventricle is deformed displaced and narrowed (visible in a pneumoencephalogram) and there is hydrocephalic enlargement of the aqueduct and of the third and lateral ventricles in the late stages The tumor is vascular and the surrounding cerebrospinal fluid has a high protein content (cerebrospinal fluid protein of 300 mg per cent or over is not infrequent) The microscopic picture is that of a typical neurofibroma (axis cylinders mixed with masses of fibrous connective tissue in interlacing strands palisaded nuclei and mononuclear giant cells without mitoses) The typical clinical syndrome which usually occurs in adult men or women is tinnitus deafness and rotational vertigo [seldom in discrete attacks as in Meniere s syndrome (see p 273)] of several years standing followed by stiff neck and postauricular or suboccipital pain spasms and twitching or slight weakness of the face paresthesias or pain in the face dysphonia and dysphagia and homolateral cerebellar ataxia of the arm and leg Headache vomiting and choked disk are late findings Variations of this syndrome are numerous Early in its development only progressive deafness tinnitus and vague vertigo may be present and the abnormal audiogram impaired vestibular function elevated cerebrospinal fluid protein widened in

factors As a general rule unless an operation is performed almost all intracranial tumors end fatally Death in most instances is preceded by a critical rise in intracranial pressure and tentorial or foramen magnum herniation The more malignant tumors such as the glioblastoma multiforme medulloblastoma and metastatic carcinoma end fatally within a year as a rule whereas the slowly growing meningiomas and astrocytomas often permit survival for many years

The prospects for recovery after surgery depend largely upon the type of tumor With meningiomas and acoustic neurofibromas if completely excised there may be a complete cure In gliomas the outlook is more bleak Cure is rare for seldom can complete excision be accomplished Nevertheless with the slow growing gliomas partial excision the marsupialization of a cyst the relief of increased intracranial pressure may lead to improvement and resumption of a useful life for many years With metastatic growths the outlook is dismal though if there are no metastases in other organs and the cerebral deposit appears to be solitary operation has occasionally resulted in temporary recovery for a few months or a year or two

Treatment

The treatment of primary intracranial tumors is surgical removal Unless the patient is old or suffers some other disease which threatens to take his life within a few months the brain tumor should be exposed by craniotomy and biopsied This craniotomy which usually carries a mortality rate of 2 to 5 per cent should be undertaken only when the diagnosis of an intracranial space occupying lesion is clearly established by clinical symptoms and signs and confirmed by one or more special diagnostic procedures The latter should be kept at a minimum arteriography and ventriculography are in themselves hazardous particularly if done when intracranial pressure is high and they add to the mortality from craniotomy

The premium on early diagnosis is not so great as in tumors elsewhere in the body In the vast majority of patients there is little prospect that an early diagnosis and operation will improve the surgical result or effect a cure The benign surface tumors grow so slowly that one can usually temporize for weeks or months if diagnosis is uncertain without significantly worsening the surgical outcome providing of course that the operation is not delayed until high intracranial pressure has developed If the tumor is a glioma the prospect of complete eradication even with early operation is almost nil hence little is lost by waiting a few weeks or months providing the patient is not permitted to become comatose before being transferred to the neurosurgeon in which instance the chances of surviving the operative procedure are poor By waiting for the clinical syndrome to evolve one avoids diagnostic errors (confusion of tumors with other diseases)

The physician s responsibilities in this field of intracranial tumors are (1) diagnosis—he must separate the tumor cases from all the others which pass through his hands (2) exclusion of the possibility that the intracranial mass is part of a general disease which would contraindicate surgery i e metastatic carcinoma syphilis tuberculosis parasitic infections etc (3) exclusion of the several pseudotumor syndromes (4) maintenance of the patient in the best possible condition until surgery can be undertaken (fluids electrolytes etc) (5) assisting the surgeon in the postoperative medical management Dehydration i e use of hypertonic solutions [$MgSO_4$ by mouth or rectally or 50 per cent sucrose by vein (cf p 1618)] may be of help as a palliative measure in tiding the patient over a bout of intracranial hypertension In inoperable cases the objectives are to maintain the morale of the family and patient as long as possible and to provide intelligent supportive therapy

In general although the results of therapy are frequently disappointing there are always the few dramatic successes that serve as a perpetual stimulus to the physician and so it is always with the next patient that he hopes to achieve a cure

SPINAL CORD TUMORS

Growths and other space occupying lesions within the spinal canal can be conveniently divided into two groups those which arise within the substance of the spinal cord and invade and destroy tracts and central gray structures (intramedullary) and those which arise outside the spinal cord (extramedullary) from the vertebral bodies and epidural tissues (extradural) the meninges or roots (intradural) The relative frequency of spinal tumors in these different locations in a general hospital is about 5 per cent intramedullary 40 per cent intradural extramedullary and 55 per cent extradural The percentage of extradural lesions is usually higher than in most neurosurgical series (e g Elsberg s figures of 10 67 and 15 per cent respectively) which often do not include many of the lymphomas metastatic carcinomas etc most of which are extradural

The cellular origin of the intramedullary gliomas has been mentioned in the section on intracerebral tumors The proportions of the different cell types differ however Kernohan who has had one of the largest series of pathologic cases found all the gliomas represented in the spinal cord but ependymoma was noted to make up 40 per cent and the remainder were more or less evenly distributed

mors of the optic nerve and angiomas of the orbit must be considered in the differential diagnosis Auscultation of the skull x ray of the skull and carotid arteriography are helpful in differentiating these lesions

MENINGIOMA OF THE OLFACTORY GROOVE This tumor is a growth derived from arachnoidal cap cells along the cribriform plate The diagnosis depends on the finding of ipsilateral or bilateral anosmia ipsilateral or bilateral blindness often with optic atrophy on one side and papilledema without atrophy on the other (Kennedy syndrome) and mental changes The tumors may reach enormous size before coming to the attention of the physician The anosmia if unilateral is rarely if ever reported by the patient The unilateral visual disturbance may consist of a slowly developing unilateral central scotoma Confusion forgetfulness inappropriate jocularity (*Witzelsucht*) are the usual psychic disturbances The patient is indifferent to or jokes about blindness Usually there are x ray changes along the cribriform plate and an extremely high cerebrospinal fluid protein (200 to 400 mg)

GLIOMA OF THE BRAIN STEM Astrocytomas of the *brain stem (formerly called bipolar spongioblastomas)* are slow growing firm white infiltrating growths which insinuate themselves between tracts and nuclei They produce a variable clinical picture depending on their exact location in the medulla pons and midbrain (Chaps 30 and 254 for these syndromes) The characteristic features in the early stages are signs of crossed motor or sensory disturbances which always indicate brain stem disease and as the lesion advances an orderly suc*cession of new signs due to involvement of neigh*boring structures and finally signs of bilateral disease in the brain stem Headache vomiting and papilledema occur late The course is slowly progressive over years unless some part of the tumor becomes more malignant (glioblastoma multiforme) in which instance the illness may terminate fatally within months The main clinical problem is to differentiate between this disease multiple sclerosis and vascular malformations of the pons These so called intramedullary or intrinsic brain stem lesions may usually be distinguished from extramedullary compressive ones by (1) predominance of both tract and nuclear involvement in the former and of cranial nerve involvement in the latter (2) signs of involvement of special intramedullary structures e g internuclear ophthalmoplegia due to affection of medial longitudinal fasciculi or vertical nystagmus which are rarely observed in compressive lesions of the brain stem Pneumoencephalography to visualize the fourth ventricle and *aqueduct and occasionally vertebral* arteriography are helpful in diagnosis The treatment is x ray radiation and if intracranial pressure is increased a Torkildsen ventriculo cisterna magna shunt

GLIOMA OF THE OPTIC NERVES AND CHIASM This tumor is often found in patients with von Recklinghausen s disease and like the glioma of the brain stem is most frequently observed in children and adolescents The initial symptoms are dimness of vision with constricted fields bizarre bilateral field defects of homonymous heteronymous sometimes bitemporal type blindness and optic atrophy with or without papilledema Hypothalamic signs (infantilism adiposity polyuria somnolence and genital atrophy) are common X rays reveal an enlargement of the optic foramen With this finding and the lack of ballooning of the sella or suprasellar calcification pituitary adenoma Hand Schuller Christian disease and craniopharyngioma can be excluded The treatment is surgical excision or x ray depending on the exact location

CHORDOMA This is a soft jellylike gray pink growth composed of cords or masses of large cells with granules of glycogen in their cytoplasm and often multiple nuclei and intercellular mucoid material They are locally invasive but do not metastasize They may arise from any part of the base of the cranium or vertebral column but the commonest sites are the base of the skull (from physaliphora ecchondrosis) or lumbosacral region (giving rise to a cauda equina syndrome) Those in the base of the skull create a remarkable clinical picture in which all or any combination of cranial nerve palsies from II to XII on one or both sides are combined with a retropharyngeal mass and erosion of the clivus of sphenoid bone and the occiput It is one of the four *tumors that may present both as an intracranial* and as an extracranial mass (The other three are the neurofibroma the glomus jugulare tumor and carcinoma of sinuses or pharynx) The treatment is x ray therapy

NASOPHARYNGEAL GROWTHS WHICH ERODE THE BASE OF THE SKULL These are rather common in a general hospital and arise from the mucous membrane of the paranasal sinuses or the nasopharynx near the eustachian tube i e the fossa of Rosenmueller (*transitional cell carcinoma Schmincke tumor*) In addition to symptoms of nasopharyngeal or sinus disease which may not be prominent facial pain and numbness (trigeminal) abducens palsy (sixth cranial nerve) and other cranial nerve palsies may occur Diagnosis depends on inspection and biopsy of a nasopharyngeal mass biopsy of an involved cervical gland and x ray evidence of erosion of the base of the skull The treatment is x ray therapy

Prognosis

The prognosis of intracranial tumor is influenced by the nature of the growth its location and other

the tenth eleventh and twelfth thoracic and the first lumbar vertebrae may result in a curious syndrome of mixed cauda equina and spinal cord symptoms Lesions of the cauda equina alone always difficult to separate from diseases of the plexus and multiple nerves are usually attended in the early stages by pain which is variously combined with an asymmetric atrophic areflexic paralysis radicular sensory loss and later sphincteric disorder This must be distinguished from tumors of the conus medullaris (lower sacral segments of spinal cord) in which there are early disturbance of sphincters of the bladder and bowel back pain hypesthesia and anesthesia over the sacral dermatomes a lax anal sphincter with loss of anal and bulbocavernosus reflexes and sometimes weakness of lower leg muscles A Babinski sign means that the spinal cord is involved above the fifth lumbar segment

Diagnosis

Several problems may arise in the diagnosis of patients with spinal cord tumors First in the early stages spinal tumor must be distinguished from other diseases which cause pain over certain segments of the body i e those affecting the gall bladder kidney stomach and intestinal tract pleura etc Here the localization of the pain to a dermatome its intensification by effort segmental sensory changes and minor alterations of motor reflex, or sensory function in the legs will usually provide the clues to the compressive irritative radicular lesion Examination of the cerebrospinal fluid x ray of the spine and myelography will settle the diagnosis in most instances

If symptoms and signs of disorder of sensory and motor tracts of the spinal cord are present there is still the problem of determining the segmental level of the lesion At first the sensory and motor deficiencies may be most pronounced in those parts of the body furthest removed from the lesion i e in feet or lumbosacral segments Later these sensory and motor levels may rise but at any time they may be far below the lesion Of greatest help here are the locality of the root pains and atrophic paralysis and lastly the upper level of hypalgesia Again myelography is necessary to determine the exact level of the cord compression If localization of the cord lesion in terms of spinal segments has been established there is still the problem of ascertaining the vertebral localization for the two do not correspond (see Chap 255 for a statement of the relationship of spinal segment to vertebrae)

Once vertebral and segmental levels are settled there is still the necessity of determining whether the lesion is neoplastic and is extradural intradural extramedullary or intramedullary This is important from the standpoint of etiologic diagnosis If there is a visible or palpable spinal deformity or x ray evidence of vertebral destruction one may confidently assume an extradural localization Without x ray changes one still suspects extradural lesion if root pain developed early and is bilateral spine ache is prominent and percussion tenderness is marked Motor symptoms below the lesions precede sensory changes and sphincter disturbances are late The distinction between intradural-extramedullary and intramedullary lesions is almost impossible Radicular pain asymmetry of signs of motor and sensory tract involvement and early cerebrospinal fluid blockage (positive Queckenstedt test and high protein) favor the extramedullary localization With extradural lesions one must differentiate between ruptured disk spondylosis (hypertrophic spurring and osteophyte formation in cervical spinal canal) tuberculous caries other pyogenic fungous or syphilitic granulomatous lesions secondary carcinoma or lymphoma With intradural-extramedullary lesions meningioma neurofibroma meningeal carcinomatosis cholesteatoma, teratomatous cyst or meningomyelitic process is most likely Intramedullary lesions are usually gliomas or vascular malformations A negative Queckenstedt test normal or relatively low protein in cerebrospinal fluid and a negative myelogram will serve to rule out intraspinal tumors or granulomatous lesions in most instances

In conclusion it is well always to remind oneself that of the more than 30 diseases of the spinal cord there are available effective means of treating only a few—extramedullary spinal cord tumors syphilis (meningomyelitis and tabes) epidural granulomas (pyogenic tuberculous fungous) subacute combined degeneration and nutritional myelopathy The physician s major responsibility is to determine whether or not his patient has one of the treatable diseases If not exact diagnosis is a matter only of academic interest

Treatment

This varies with the nature of the lesion and the clinical condition of the patient Intradural-extramedullary tumor should be removed Laminectomy decompression marsupialization of cysts and x ray therapy is the treatment of intramedullary gliomas Extradural malignant growths are best managed by the use of opiates for pain x radiation endocrine therapy (for carcinoma of breast and prostate) nitrogen mustard (for certain lymphomas) Sometimes laminectomy and decompression are necessary for diagnosis and prevention of irreversible compressive effects and infarction of the spinal cord With tuberculous caries immobilization of the spine in hyperextension and streptomycin therapy are indicated and laminectomy should be reserved for exceptional cases with complete and irreversible

amongst astrocytomas glioblastomas oligodendrogliomas ganglioneuromas medulloblastomas hemangiomas and hemangioblastomas The hemangioma is the common source of spontaneous hematomyelia and the hemangioblastoma may give rise to a syringomyelia

Pathologic Anatomy and Physiology

Peculiarities of anatomic structure are decisive factors in determining the symptomatology of tumor growths The structure of the spine was described in Chap 255 Traumatic Diseases of the Brain and Spinal Cord The spinal cord hangs as a cylinder within it being moored by the denticulate ligaments and spinal roots There is a small space between the dura and vertebral column which contains fat and a venous plexus and is in communication with extradural tissues through the intervertebral foramens Epidural growth—whether arising as direct extensions from the vertebral bodies by hematogenous dissemination in epidural fat or extension through intervertebral foramens from an extraspinal tumor—may displace and finally compress the spinal cord Masses within the spinal canal may also interfere with its circulation either by blocking the collateral vessels which enter through the intervertebral foramen along the roots or by direct compression of the veins which course longitudinally on the surface of the spinal cord

Intramedullary growths both invade as well as compress and distort fasciculi in the adjacent white matter As the cord enlarges from the tumor growing within it or is compressed from a tumor growing without the free space around the cord is consumed and the cerebrospinal fluid below the lesion becomes isolated or loculated from the rest of the so called circulating cerebrospinal fluid above This can be demonstrated by a positive Queckenstedt test (p 294) Froin s syndrome and interruption of the flow of pantopaque in the subarachnoid space (myelogram)

Symptomatology

Patients with spinal cord tumor are likely to manifest one of two clinical pictures one a radicular spinal syndrome nearly always painful the other a purely sensorimotor spinal tract or rarely a syringomyelic syndrome

Spinal Cord Compression The predominant clinical syndrome relates to spinal cord compression With intraspinal tumors the onset of the compressive symptoms is usually gradual over a period of weeks or months and the course is progressive The initial disturbance is likely to be motor and often the distribution is asymmetric With cervical lesions the order of motor impairment is first the arm then the leg on the same side next the opposite leg and finally the opposite arm With thoracic lesions one leg usually becomes weak and stiff before the other one Subjective sensory symptoms (tingling paresthesias) of spinal tract type take the same pattern Pain and temperature are more likely to be affected than touch vibration and position senses and are contralateral to the maximum motor weakness (Brown Sequard syndrome) Nevertheless the posterior columns are also frequently involved The bladder and bowel usually become paralyzed coincident with motor paralysis of the legs If the compression is relieved there is recovery of these members of the body in the reverse order of their affection the first part affected being the last to recover and sensory symptoms disappearing before motor

Compressive irritative Radicular Syndrome This syndrome of spinal cord compression is often combined with radicular pain i e pain in the distribution of a spinal root It is described as knifelike or as merely a dull ache with superimposed sharp pains which are intensified by cough sneeze or strain and radiation in a distal direction i e away from the spine Segmental sensory changes (paresthesias hyperalgesia impairment of pain and touch) or motor disturbances (spasm cramp twitching atrophy fascicular twitching and loss of tendon reflex) and an ache in the spine are the usual manifestations of a compressive irritative lesion of roots Tenderness of spinous processes over the growth is found in half the patients These segmental changes particularly the sensory ones often precede the signs of spinal cord compression by months or years if the lesion is benign Sphincter disturbances usually appear late

The clinical findings upon examination are spastic weakness of the legs in one leg more than in the other with thoracolumbar lesions and of the arms and legs with cervical lesions a sensory level for pain on the trunk below which pain sense is reduced or lost posterior column signs and a spastic bladder under weak voluntary control

The diagnosis is established by x rays of the spine (erosion of vertebrae widened spinal canal) lumbar puncture and electromyography to demonstrate the fasciculations resulting from involvement of motor roots But the most important diagnostic test of all is Pantopaque myelography for the direct visualization of the compressive lesion Although necessary procedures lumbar puncture and myelography may occasionally exacerbate the symptoms and signs

Special Spinal Syndromes Unusual clinical syndromes may be found in patients with tumors near the foramen magnum *They may produce a quadriparesis* with pains in the back of the head and stiff neck a weakness and atrophy of the hands and dorsal neck muscles and either bizarre sensory changes or no sensory loss whatsoever Lesions of

1 Acute disseminated encephalomyelitis
2 Acute necrotizing hemorrhagic encephalomyelopathy (acute hemorrhagic leukoencephalitis)
3 Multiple sclerosis
4 The neuromyelitis optica syndrome
5 Diffuse cerebral sclerosis

Future investigation may reveal that necrotizing encephalomyelopathy is merely a severe form of disseminated encephalomyelitis and that the neuromyelitis optica syndrome is a variant of the latter disease or of multiple sclerosis It is also possible that in due course certain cases now regarded as acute multiple sclerosis may come to be recognized as constituting another form of disseminated encephalomyelitis However in the absence of concrete evidence the above disorders will be considered individually although it is recognized that at least some of them may be artificially defined

ACUTE DISSEMINATED ENCEPHALOMYELITIS

This term includes cases of postexanthematous postvaccinal and postinfective encephalomyelitis the condition may also be referred to as acute perivascular myelinoclasis In its most typical form it follows vaccination against smallpox and inoculation against rabies In such cases the clinical manifestations follow a relatively stereotyped pattern this is much less true of the encephalomyelitic complications of the exanthems of childhood in which in addition the time relationship to the onset of the exanthem is not so clearly defined Within recent years this group has been broadened to include cases showing encephalitic and/or myelitic manifestations subsequent to nonspecific infective illnesses Adams and Kubik have shown that under such circumstances the pathologic changes are essentially the same as those in the more clearly defined syndromes referred to above

Definition. Acute disseminated encephalomyelitis may therefore be defined as an acute encephalitic and/or myelitic disorder of variable course and severity which is characterized clinically by symptoms indicating damage chiefly to the white matter of the brain and/or spinal cord and pathologically by perivascular cellular infiltration and perivenous demyelination The syndrome may follow smallpox vaccination antirabic inoculation or a nonspecific infective illness (sometimes vaguely referred to as "influenzal") or may develop during the course of an exanthem occasionally it may occur with no clear history of preceding or concurrent infection

Pathology Naked-eye examination of the brain and spinal cord reveals no distinctive changes save for vascular congestion of doubtful significance Microscopically the white matter shows innumerable small zones of demyelination from 0 1 to 1 0 mm in diameter which invariably surround small or medium sized veins Conspicuous subpial demyelination is a prominent feature and is probably related to the profusion of small veins in these situations a similar relationship can also be adduced to explain the areas of subependymal demyelination which are frequently seen around the third and lateral ventricles Silver stains generally demonstrate the integrity of the axis cylinders within the lesions though they may be damaged as shown by their tortuosity and thickening Reacting microglial cells are seen in the demyelinated areas and there is also perivascular infiltration with lymphocytes histiocytes and plasma cells sometimes slight and sometimes massive Meningeal infiltration although invariable is rarely marked. Detailed observation reveals that nearly all the lesions are of the same age and that they are usually scattered throughout the length and breadth of the nervous system indicating simultaneous involvement of the entire neuraxis In other instances however they may be more severe in one part of the nervous system than another thus determining the primarily encephalitic or myelitic nature of the illness It is of course likely that in cases which recover the pathologic changes are less widespread and severe and there is evidence to show that they may be almost, if not entirely reversible

Etiology In this form of demyelinating disease above all, there is much evidence to suggest that one is dealing with an allergic response of the nervous system to an unidentified antigenic agent The main support for this hypothesis lies in the close resemblance of the pathologic findings in such cases to those observed in experimental allergic encephalomyelitis

Clinical Manifestations In view of the pleomorphism of the clinical picture of disseminated encephalomyelitis depending as it does upon the nature of the primary disease which it complicates it will be convenient to subdivide this section with reference to identity of the preceding or concurrent infection

Postvaccinal Encephalomyelitis Encephalomyelitis following antismallpox vaccination is by far the commonest disorder of this type though an identical syndrome may follow inoculation against rabies and a similar illness may rarely occur after smallpox itself A number of epidemics of the post vaccinal type occurred in Holland and England in the 1920s, when it became evident that the disorder affected both sexes equally was commonest in children of school age and was much more frequent after primary vaccination than revaccination. In Holland it affected roughly one person in every 2 300 primary vaccinations and one in every 50 000 revaccinations

In most instances the disease develops between

spinal block Immobilization of the neck and later a collar (Thomas or other) is the treatment of choice in spondylosis Only in a rapidly advancing compressive spinal cord syndrome in a relatively young person should there be a laminectomy and cutting of the denticulate ligaments

TUMORS OF THE PERIPHERAL NERVES

These tumors are discussed in Chap 260

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257 DEMYELINATING DISEASES

John N Walton

It is well recognized that there exists a large and important group of diseases of the nervous system all of which are characterized pathologically by a destructive process involving the myelin sheaths of nerve fibers Despite this single common feature there are numerous variations in the clinical manifestations and in the severity and distribution of the pathologic changes which serve in typical cases to distinguish the several disease entities within the group Nevertheless it may at times be impossible to classify an individual case with certainty so ill-defined are the clinical and pathologic margins which separate the constituent disorders

CLASSIFICATION

Any classification of diseases in medicine must depend upon a combination of evidence from three sources one etiologic another clinical and the third pathologic The lack of clear definition in any one of these three fields has led to the difficulties now experienced when attempting to classify the demyelinating diseases Although a familial incidence has been observed occasionally there is no clear evidence to suggest that genetic factors play a fundamental part in their *causation It is also* true that while many theories of etiology—infective metabolic allergic and vascular—have been invoked none conforms entirely to the observed facts *An allergic* process seems very probable in cases of acute disseminated encephalomyelitis and *may well be the basis of the disease state in* other conditions within the group but knowledge is still incomplete so that in most instances the etiology remains obscure Clinically there is no doubt that the natural history of the illness in a chronic relapsing case of multiple sclerosis is entirely different from that observed in say acute disseminated encephalomyelitis following measles On the other hand a distinction on purely clinical grounds between acute multiple sclerosis and subacute encephalomyelitis may be impossible the existence of such transitional and borderline cases precludes a classification based entirely upon clinical criteria

Similar difficulties arise in considering pathologic data In general the basic process is one of destruction of myelin sheaths with relative sparing of nerve cells axis cylinders and supporting structures however the distribution and severity of the lesions vary greatly In one disease the foci may be multiple small and widely disseminated in another they are large and spreading outward from one or a few centers sometimes they are all perivenous but in other cases this is only partially true Whereas in one instance the axis cylinders are virtually intact despite severe myelin destruction in another they may suffer to an almost equal extent From the pathologic as well as the clinical standpoint intermediate or transitional changes may be seen bridging the gap between disease entities which have been customarily though artificially defined The source of these difficulties springs from the probability that myelin destruction is not the primary process but merely a response of the nervous system to a variety of noxae Definition of such etiologic factors if achieved must surely lead to a clearer understanding of the clinical and pathologic changes observed and in turn to a firm classification In the meantime correlation of the available information from all sources would support the following classification as the most practical

a transient illness occurs with headache drowsiness and neck stiffness in others there may be a severe ataxia and occasionally athetotic movements while in yet others the typical picture of transverse myelitis develops Whatever the clinical manifestations the prognosis is good death is uncommon and over 90 per cent of patients make a complete recovery

In postexanthematous cases as in the postvaccinal the cerebrospinal fluid may rarely be normal but usually contains an excess of lymphocytes and protein. Diagnosis is comparatively easy in the presence of the exanthem

Postinfective Encephalomyelitis. This group includes a heterogeneous collection of cases in which an encephalomyelitic illness succeeds a respiratory tract infection or an influenzalike illness it is probably desirable that it should be broadened yet further to embrace cases of similar clinical course showing identical pathologic features in which there is no history of a preceding illness

The clinical manifestations in cases in this group may vary from the typical picture of severe disseminated encephalomyelitis with deepening coma and flaccid paraplegia on the one hand to a mild illness with headache drowsiness fever and perhaps transient limb or bulbar pareses on the other Myelitic syndromes may occur though in a considerable proportion of these cases the disease process also affects the brain stem giving nystagmus impairment of ocular movement dysphagia, facial weakness and variable long tract signs Evidence of nerve root involvement is common in cases where the disorder is primarily spinal and the condition may then resemble the closely related idiopathic polyneuritis (Guillain-Barre syndrome) In many other cases there will be a striking resemblance to the accepted clinical manifestations of acute multiple sclerosis However a follow up study carried out by Miller and Evans on cases of this type has shown that they do not develop further neurologic episodes during the succeeding years

Cerebrospinal fluid changes as in the other forms of acute encephalomyelitis are not diagnostic and in these cases particularly those with no history of preceding infection diagnosis may be very difficult. The development of coma and flaccid quadriplegia following an influenza like illness is distinctive but on other occasions virus encephalitis multiple sclerosis and bulbospinal poliomyelitis may be mimicked. Indeed accurate diagnosis may depend in the last resort upon pathologic evidence and even this *may fail to distinguish the condition* from multiple sclerosis In the present state of knowledge it is difficult to glean accurate information about prognosis A considerable proportion of comatose and quadriplegic patients die those in whom the neurologic signs are relatively mild usually recover but in the intermediate group it is impossible to predict with certainty which patients will be left with residual evidence of neurologic deficit

Treatment In an attempt to prevent the occurrence of postvaccinal encephalomyelitis some authorities consider it unwise to carry out primary *vaccination in a young adult unless he has been* in contact with a case of smallpox, or during an epidemic. This view is not generally accepted. Other prophylactic measures are probably of little avail.

Benefit has been claimed for the administration of immune human serum 10 ml intravenously both in cases appearing after vaccination and in those following or complicating the exanthems failing this an intramuscular injection of immune citrated whole blood may be given Numerous workers also pay tribute to the value of daily or twice daily lumbar punctures Recent work has suggested that cortisone and ACTH have a beneficial effect. Despite the difficulty of carrying out accurately controlled trials in order to assess results it seems sensible to use one or another of these remedies

ACUTE NECROTIZING HEMORRHAGIC ENCEPHALOMYELOPATHY

In a small number of patients dying from a fulminating encephalopathic illness certain distinctive pathologic features may be found On section of the brain, the white matter of one or both hemispheres is seen to be destroyed almost to the point of liquefaction The involved tissue is pink or yellowish gray and flecked with multiple small hemorrhages Sometimes similar changes are localized to the brain stem On histologic examination one finds widespread necrosis of small blood vessels necrosis of brain tissue around the vessels with intense cellular infiltration, multiple small hemorrhages and a violent inflammatory reaction in the meninges The pathologic picture resembles disseminated encephalomyelitis in its perivascular distribution and diffuse sclerosis in its tendency to congregate into large foci in the cerebral hemispheres

The clinical course of the illness resembles acute disseminated encephalomyelitis save for its apoplectiform onset and rapidity of progress leading often to death within 48 hr it is also true that neurologic signs are frequently unilateral or purely bulbar in type reflecting the localized nature of the pathologic process It is probable that certain patients *showing an explosive myelitic illness* are suffering from a necrotizing myelitis of similar type but pathologic evidence in support of this view has been difficult to obtain The cerebrospinal fluid reveals a more intense reaction than in other demye-

the seventh and twelfth days after vaccination though the period may be shorter after revaccination The onset is generally abrupt with headache drowsiness fever and vomiting There may be neck stiffness and other signs of meningeal irritation at this stage while convulsions are occasionally seen Soon afterwards signs of spinal cord involvement usually appear with flaccid paralysis of the limbs which may be hemiplegic in distribution but more commonly involves all four limbs Tendon reflexes disappear and the plantar responses become extensor Sphincter control is generally lost and sensory loss though variable may be extensive and severe Nystagmus ocular palsies pupillary changes and sometimes trismus may give evidence of brain stem involvement while extension of the cerebral affection may lead to stupor and deepening coma Despite these general features of the typical case numerous variations occur less commonly so that one patient may suffer a predominantly encephalitic illness with little evidence of cord damage another may have a hemiplegia while sometimes a purely myelitic syndrome may occur with no headache neck stiffness or clouding of consciousness Less frequently still a syndrome suggesting involvement of nerve roots or even peripheral nerves may develop Usually the site of vaccination is not remarkable although a few patients show a generalized erythematous rash and others generalized vaccinia The cerebrospinal fluid almost invariably shows an increase in protein and lymphocytes but in rare cases it is normal

DIAGNOSIS The association with vaccination or inoculation will usually leave the diagnosis in little doubt and the characteristic combination of encephalitic and myelitic features will readily distinguish the condition from meningitis virus encephalitis tetanus and poliomyelitis Rarely an atypical case may mimic any one of these disorders In the radicular form there may be difficulty in differentiating the condition from idiopathic polyneuritis

PROGNOSIS Between 30 and 50 per cent of cases reported have died within 4 to 5 days of the ictus usually in deep coma with terminal evidence of medullary paralysis Improvement with recovery of consciousness and regression of neurologic signs occurs in the remaining cases and may be surprisingly complete Miller has shown however that a significant proportion of patients show residual neurologic signs intellectual impairment and/or psychoneurotic sequelae many years after the illness

Postexanthematous Encephalomyelitis More cases of encephalomyelitis have been described after measles than after any other exanthem but occasionally rubella and chickenpox have been complicated in this way The exact status of the neurologic complications of scarlatina whooping cough and mumps has yet to be defined Miller Stanton and Gibbons have shown that lymphocytic meningitis is the principal complication of scarlatina and mumps and in the latter condition it is probably due to invasion of the nervous system by the virus However in a proportion of cases of mumps and very rarely in scarlatina a true demyelinating encephalomyelitis may occur The encephalopathy of pertussis which is fatal in over a third of cases and may leave disabling sequelae in many others is entirely different pathologically and may be hypoxic in origin

Encephalomyelitis complicating *measles* generally begins 2 to 4 days after the appearance of the rash but may antedate it and may even occur in patients with a history of contact who do not develop a rash The clinical picture is variable indeed but may resemble that described under postvaccinal encephalomyelitis indicating the presence of widespread lesions throughout the white matter of the neuraxis in various combinations The most common clinical syndrome is one dominated by convulsions and deepening coma most fatal cases fall into this group Less commonly the patient may suddenly develop a hemiplegia as if from a cerebral vascular accident or show evidence of severe cerebellar disease while occasionally there develops the clinical picture of transverse myelitis or that of polyradiculitis Athetoid movements resulting from involvement of the basal ganglions are also seen infrequently In many cases however the disease is much less severe and the patient suffers a transient encephalitic illness with headache confusion and signs of meningeal irritation About a tenth of the patients succumb to the disease or to intercurrent infection however less than half the remainder recover completely and the others remain more or less severely disabled with hemiplegia paraplegia cerebellar ataxia fits or mental impairment It is not entirely certain that all the neurologic complications described are truly encephalomyelitic and in some cases cerebral vascular disease particularly thrombophlebitis may be responsible

In *rubella* a diffuse and fatal encephalomyelitic illness may rarely occur and in other uncommon cases a syndrome suggestive of polyradiculitis has been described but more often a mild and transient encephalitic illness develops The neurologic complications of *chickenpox* are similarly benign and usually occur in the second week after the rash has appeared though they can arise at the onset of the illness It is possible that in some cases the varicella virus which is closely related to that of herpes zoster is directly responsible for the patient's symptoms There is no doubt that in others characteristic perivenous lesions unlike those of virus infection have been observed In most cases

tiple sclerosis or that in other cases they have been responsible for producing a relapse Nonspecific and specific febrile illnesses pregnancy surgical opera tions trauma lumbar puncture and many other factors have been invoked from time to time An increasing volume of statistical evidence suggests that pregnancy and lumbar puncture have no in fluence upon the course of the disease but Mc *Alpine and Compston believe* that there is some times a significant relationship between infective illness or local trauma on the one hand and onset or relapse on the other There also seems to be little doubt that the onset of the disease or a relapse may occasionally appear to be precipitated by emotional stress

Incidence Multiple sclerosis is a common dis ease in Europe being particularly prevalent in Switzerland and Scandinavia *It occurs less fre* quently on the American continent and is rare in Africa and Asia It is commonest in the white races but does occur in the Negro

It affects the two sexes approximately equally and usually begins between the ages of twenty and forty some cases develop in the second decade and an increasing number are being re ported in which the onset was in the forties or fifties

Clinical Manifestations *Chronic Relapsing Type* Given a clear understanding of the pathologic changes outlined it will be evident that the clinical features of the disease may be very variable de pending upon the situation and intensity of the lesions It is clear that if it begins with a single discrete lesion there may be a great variety of presenting symptoms depending upon its site on *the other hand* if multiple *lesions occur simultane* ously in eloquent areas of the nervous system a much more specific clinical picture will result This variation in spatial distribution of the areas of demyelination is responsible for the remarkable clinical pleomorphism of the disease to which any experienced neurologist will attest Symptoms at tributable to a single lesion almost invariably remit to be followed by other manifestations at a later date *the same is largely true of other cases in* which there is clinical evidence of multiple lesions initially but in which the onset is acute In cases of these two types numerous relapses may occur each followed by a remission but each leaving in its wake further evidence of permanent neurologic deficit upon which every succeeding acute mani festation is superimposed As a rule such a patient eventually reveals a clinical state indistinguishable from that observed in another type of case which from the start can be recognized as harboring multiple disseminated lesions all progressing inex orably at much the same rate The relapsing type with multiple acute and subacute episodes is of course commoner in younger patients while the slowly progressive form is most frequent in pa tients whose disease begins in middle age in these latter individuals the major burden of the disease process generally falls upon the spinal cord

Having mentioned these general features it may be said that numerous characteristic symptom com plexes may be recognized as occurring within the structure of the disease process and are best classi fied according to the mode of onset It should be stressed that despite the variability of initial ex pression of the disease most cases after a greater or lesser period of time follow a final common path of increasing spasticity immobility respiratory or urinary infection and death McAlpine believes that in a small proportion of cases the disease may be arrested spontaneously

The more common symptom complexes observed in this disease are outlined below

1 TRANSIENT WEAKNESS OR LOSS OF CONTROL OF THE LIMBS This symptom may involve one limb (monoparesis) or both limbs on the same side (hemiparesis) but more often both lower limbs are involved (paraparesis) The patient has diffi culty in walking or in using the affected limbs and physical examination during the episode reveals evi *dence of corticospinal tract and/or cerebellar* dis ease These early manifestations frequently resolve completely only to be succeeded by others after months or years

2 VISUAL SYMPTOMS Sudden loss of vision in one eye (due to retrobulbar neuritis) or diplopia are common initial symptoms of this disease and invariably remit sometimes as long as 20 years may elapse before other features develop

3 SENSORY SYMPTOMS *The* disease may begin with numbness and paresthesias in a limb or limbs and these symptoms being transient may well be overlooked The so called useless hand syndrome in which the patient complains of clumsiness or uselessness of the hand lasting for some days or weeks must be included in this group being gen erally due to impairment of position sense from a lesion in the posterior column of the cord Less fre *quently there may be symptoms* to suggest loss of temperature sensation in one lower limb and the patient is found to have a partial Brown Sequard syndrome due to a plaque in one lateral column These manifestations too almost invariably remit

4 SLOWLY PROGRESSIVE CLUMSINESS AND WEAK NESS OF LIMBS In certain young patients the dis ease may be slowly progressive without clinical remission and in such individuals there is usually evidence of widespread *lesions most often they* show temporal pallor of the optic disks nystagmus cerebellar ataxia and weakness and spasticity of the limbs In the commoner intermittently progressive type which begins in middle life the corticospinal

linating diseases showing a polymorphonuclear pleocytosis and a considerable increase in protein

The etiology and essential nature of this condition remain obscure but the resemblance to the other demyelinating diseases should be noted a resemblance which is strengthened by the fact that certain cases showing the typically fulminating clinical picture have recovered some completely others with neurologic sequelae of variable severity The points of similarity are probably sufficient to suggest that ACTH or cortisone treatment should be tried in cases of this type

MULTIPLE SCLEROSIS

Multiple sclerosis commonly termed *disseminated* or *insular sclerosis* or *sclérose en plaque* is one of the commonest chronic neurologic diseases While pleomorphic in its clinical presentation numerous symptom complexes have come to be recognized as characteristic of the disease so that usually diagnosis is a matter of little difficulty On the other hand many acute cases show notable clinical and pathologic affinities with disseminated encephalomyelitis and with the syndrome of neuromyelitis optica Despite this lack of definition of the borderline case much less is known concerning the etiology of multiple sclerosis than is the case with the acute demyelinating disorders previously described

Definition Multiple sclerosis may be defined as a disease of obscure etiology characterized clinically by symptoms indicating the presence of multiple lesions in the white matter of the brain and spinal cord In most cases there are relapses interspersed with long periods of remission but in others it presents as an intermittently progressive disease with paraplegia and added cerebellar and brain stem signs the latter state is also the eventual outcome of the relapsing cases Pathologically there are multiple plaques of demyelination and gliosis of varying age throughout the central nervous system

Pathology Since the original description of the pathologic changes in this disease by Cruveilhier in 1835 and Carswell in 1838 there have been numerous valuable presentations notably those of Dawson Hassin Zimmermann and Netsky and Adams and Kubik Macroscopically the brain and spinal cord generally show no evidence of disease but the surface of the spinal cord may feel uneven On section numerous scattered lesions are seen which are slightly depressed and by virtue of their pinkish gray appearance (due to loss of myelin) stand out in contrast with the surrounding white matter The lesions may vary in diameter from 1 mm to several centimeters they affect principally the white matter and the roots of cranial nerves but also encroach frequently on cerebral gray matter much less often spinal roots and spinal gray matter are involved The lesions appear to have a predilection for the optic nerves and chiasm and the paraventricular areas of the brain while in the spinal cord the subpial region is often predominantly affected

The histologic appearances depend upon the age of the lesion Relatively recent lesions show a predominantly perivenous distribution of the demyelination with sparing of axis cylinders degeneration of oligodendroglia neuroglial reaction and perivascular infiltration with mononuclear cells Later large numbers of microglial phagocytes infiltrate the lesion as astrocytes in the locality increase in number and size A long standing lesion on the other hand will show thickly matted relatively acellular fibroglial tissue with only occasional perivascular macrophages in such a lesion intact axis cylinders may still be discovered but many are destroyed and this in turn leads to descending and ascending degeneration of long fiber tracts All gradations of pathologic change between these two extremes may be found in lesions of variegated size and shape Save in the most acute cases the distribution is not so strikingly perivenous as it is in disseminated encephalomyelitis

Etiology Little concrete information is available concerning the etiology of this disease save for its occasional familial incidence Pratt Compston and McAlpine have shown conclusively that it occurs in more than one member of a family more often than could be accounted for by chance This should not be taken to indicate that the disease is transmitted as a genetic trait but rather it suggests that there may be an inherited predisposition making an individual more susceptible to the unknown agent or agents responsible for the demyelinating process

None of the numerous theories advanced to explain this disease has been validated Infection by a spirochete or filtrable virus has been adduced and it has been suggested that thrombosis of venules is responsible while other workers on the basis of an analogy with sway back disease of sheep have suggested copper deficiency as an etiologic factor Yet other investigators claim to have demonstrated abnormal enzymes or poisoning with lead The very multiplicity of theories pays tribute to the lack of concrete evidence and recent experimental work has added little that is conclusive Lumsden believes that degeneration of the oligodendrocytes may be the primary factor in producing demyelination but this too is open to confirmation There is far less evidence to support the role of allergy as a causative agent in multiple sclerosis than in the case of disseminated encephalomyelitis

Precipitating Factors It has been suggested frequently that various infective and traumatic agencies have provoked the initial symptoms of mul

trophic lateral sclerosis and subacute combined degeneration may be closely mimicked but the presence of muscle wasting and fasciculations will identify the former and the latter can be confirmed by the absence of acid from the gastric juice by the anemia in most cases and by the presence of megaloblasts in the bone marrow

Cases with a progressive spastic paraplegia may be suspected of having an intrathecal neoplasm or cervical spondylosis Pain and extensive sensory loss are common in the former and rare in multiple sclerosis in which muscle wasting due to anterior horn or spinal root involvement (as sometimes seen in spondylosis) is almost unknown Basilar impression of the skull or platybasia must also be considered but in such patients there is characteristic shortening of the neck and radiographs of the base of the skull are diagnostic Careful clinical appraisal will usually lead to accurate diagnosis but in occasional cases the problem can be resolved only by recourse to cerebrospinal fluid examination radiography of the spinal canal and myelography

PROGNOSIS The duration of the disease is variable Some patients die within a few months others live 30 years or longer In general patients whose disease runs a relapsing course live longer but accurate prediction of the progress in an individual case is impossible The average total duration from the time of the first symptom is 15 to 20 years The final state of the bedridden incontinent patient racked by painful flexor spasms of the lower limbs and shaken by febrile episodes of intercurrent infection is one of the most distressing in medicine it is fortunate that many individuals retain their euphoria to the end

TREATMENT Despite the large number of remedies which have been tried no drug therapy appears to have any influence on the course of the disease ACTH and cortisone appear to be of no value and claims for the efficacy of arsenicals vasodilators and a low fat diet have not been substantiated

The most that can be done is to encourage and reassure the patient through moderate exercise and supportive measures and to keep him mobile and actively employed for as long as possible During an acute episode of the type which invariably remits it is surely preferable to assure the patient that he will recover and to preserve silence on the subject of relapse in view of the long periods of remission which may occur No patient with this disease should be told its nature until the fact becomes self evident and even when all hope of remission seems past the patient should be advised that improvement is still possible

In the late bedridden stage little can be done beyond meticulous care of the skin bladder and bowels but vigorous administration of analgesics or sometimes even rhizotomy or cordotomy may be required to ease the pain of flexor spasms in the legs

THE NEUROMYELITIS OPTICA SYNDROME

This disorder also referred to as *diffuse* or *disseminated myelitis with optic neuritis ophthalmoneuromyelitis* and *Devic s disease* is probably not a distinct nosologic entity as it resembles on the one hand multiple sclerosis and on the other disseminated encephalomyelitis and necrotizing encephalomyelopathy Clinical surveys of patients presenting with this syndrome tend to favor its identification as a form of multiple sclerosis but pathologic studies of fatal cases particularly those in which cavitation of white matter is found have often revealed a more acute and uniformly severe destructive process than is usually seen in the latter disease In the absence of any authoritative evidence to indicate in which group the condition rightly belongs it will be considered as a clinical syndrome with full recognition of the fact that its exact nature is not yet established

Definition Neuromyelitis optica is a syndrome produced by a subacute demyelinating process involving the optic nerves and spinal cord this process may be self limiting and reversible or may be progressive

Pathology To the naked eye the optic nerves and spinal cord are often soft swollen and congested Microscopy reveals extensive demyelination in the optic nerves and chiasm and a similar process is seen in the spinal cord sometimes localized to a few cervical segments and sometimes more extensive Axis cylinders are relatively intact though swollen and irregular there is microglial reaction in and around the demyelinated areas and perivascular infiltration with mononuclear cells is seen

Clinical Manifestations The syndrome affects the sexes equally and can probably occur at any age even during the first decade of life In the so called typical case there is often pain in the eyes followed by impairment of vision first in one eye but affecting the other within a few hours or days Visual loss is variable in extent characteristically there are bilateral central scotomas but total blindness may occur and one eye may be more severely affected Papilledema is sometimes seen but the optic disks often look normal Soon afterwards the characteristic picture of a transverse myelitis appears with flaccid paralysis loss of sphincter control absence of tendon reflexes and extensor plantar responses and variable sensory loss in the extremities depending on the level of the lesion The sensorium is not affected Occasionally the spinal cord syndrome precedes the visual disturbance It is possible that certain cases of bi

tracts are predominantly affected though there is usually some loss of position and vibration sense in the lower limbs indicating posterior column in addition to lateral column disease

5 SYMPTOMS OF PRIMARY BRAIN STEM INVOLVEMENT Some patients may present evidence of predominantly cerebellar disease and it is often these individuals who show Charcot s triad of nystagmus scanning or syllabic speech and intention tremor this form is somewhat uncommon Another group of cases may suffer a transient episode of severe vertigo and vomiting because of a lesion affecting the vestibular connections and may then go for years before other symptoms develop The same is generally true of patients showing evidence of a pontine lesion some of whom may have transient facial anesthesia followed months later by tic douloureux and later still by evidence of spinal cord disease on other occasions tic douloureux may develop in a patient showing overt manifestations of the disease

Acute Multiple Sclerosis Occasionally cases of multiple sclerosis run an acute or subacute course leading to death in weeks or months or else a series of symptoms may develop rapidly and then remit partially or completely to be followed by characteristic relapses In some such individuals the onset is marked by headache vomiting and delirium and by a succession of symptoms indicating severe involvement of the brain stem as described above or of the brain optic nerves or spinal cord In the so called cerebral cases there may be mental changes convulsions aphasia hemianopia and variable long tract signs whereas the spinal type may show the picture of a transverse myelitis These forms of the disease are uncommon and may be very difficult to distinguish from disseminated encephalomyelitis and neuromyelitis optica

Motor symptoms are generally due to corticospinal tract or cerebellar involvement or to a combination of the two Corticospinal tract disease gives a spastic gait and muscular weakness of upper motor neurone type with exaggeration of tendon reflexes in the affected limbs and extensor plantar responses Cerebellar disease results in intention tremor and clumsiness in the performance of fine coordinated movements and the gait is often characteristically broad based and ataxic Involvement of central cerebellar connections gives nystagmus on lateral gaze with the quick phase in a lateral direction

Sensory symptoms such as paresthesias and uselessness of the limbs are due to posterior column involvement and in such cases loss of position sense of two point and tactile discrimination and of vibration sense will be observed and if the changes are extensive Romberg s sign will be positive

Visual loss is due to retrobulbar neuritis which may produce pain in the eye and sometimes disk swelling vision gradually returns after weeks or months and central scotomas may persist while the temporal half of the optic disk becomes pale Such pallor is frequently seen in the absence of any history to suggest an acute neuritic episode Diplopia is occasionally due to selective involvement of one of the oculomotor nerves but more often is of central origin occurring without objective ocular palsy Paralysis of conjugate ocular deviation particularly internuclear ophthalmoplegia is frequent Horner s syndrome occurs rarely but the pupils are usually unaffected

Hysterical features are not uncommon in patients with multiple sclerosis and may make diagnosis difficult while some individuals eventually show evidence of dementia Although euphoria or pathologic cheerfulness is generallly regarded as characteristic many patients are depressed

The sphincters are often involved precipitancy of micturition is characteristic in the early stages but later there may be both fecal and urinary retention Rarely fecal incontinence occurs alone

CEREBROSPINAL FLUID A small proportion of cases particularly the more acute ones show a slight mononuclear pleocytosis The protein content may be normal but there often is slight excess of globulin The latter is most characteristic occurring in perhaps 50 per cent of cases and is indicated by an abnormal colloidal gold curve usually paretic first zone in type but occasionally mid zone in type in the presence of a negative Wassermann reaction

DIAGNOSIS In a characteristic case the evidence of wide dissemination of lesions throughout the neuraxis leaves the diagnosis in little doubt Indeed it is an axiom that the disease should not be diagnosed when all the patient s symptoms and signs can be explained by a single lesion Occasionally this rule must be ignored in the presence of one of the characteristic symptom complexes already described but it is a valuable guide For reasons already given distinction from disseminated encephalomyelitis and neuromyelitis optica is particularly difficult in the acute case but bilateral visual loss as well as stupor and coma are rare in multiple sclerosis while disseminated encephalomyelitis is a self limiting monophasic disease Other acute manifestations may mimic labyrinthitis meningovascular syphilis and encephalitis the first may be recognized only by the course of the disease and then not with certainty but cerebrospinal fluid examination will generally identify the other conditions

Confusion may occasionally arise with the familial ataxias which are generally distinguished by their familial incidence the occurrence of skeletal abnormalities and other associated genetic traits and by their stereotyped clinical pattern Amyo

The disorder often begins with slowly progressive visual failure usually affecting both eyes simultaneously but occasionally beginning unilaterally These features are succeeded by focal or general fits dysphasia mental deterioration and variable weakness of the limbs leading eventually to total blindness dementia and spastic quadriplegia On occasion the onset may be sudden with headache stupor and convulsions in which case visual failure develops later Nystagmus is common but other ocular signs are rare if the pathologic change spreads to the temporal lobe deafness may result

The cerebrospinal fluid is generally normal but may show a slight increase in protein and mononuclear cells

Diagnosis. In a child presenting with visual loss fits progressive dementia and spasticity the diagnosis is often self evident but even in such cases there may be difficulty in differentiation from cerebral lipoidosis *or subacute inclusion encephalitis* In lipoidosis e g Tay Sachs disease there will generally be a history of affection of other members of the family but diagnosis from subacute encephalitis may be impossible clinically differentiation is only of academic interest since all these disorders *are progressive and ultimately fatal* The electroencephalogram which shows paroxysmal and bilaterally synchronous slow wave complexes in subacute encephalitis and almost continuous irregular spike and wave activity in lipoidosis may be of great value in making the distinction since cases *of Schilder s disease show only diffuse slow rhythms* Cases arising in later life may be confused with intracranial tumor necrotizing hemorrhagic encephalopathy and presenile or atherosclerotic dementia few cases in this age group save those showing the classical clinical picture are diagnosed during life

Prognosis The disease is steadily progressive usually leading to death within 3 years but uncommonly patients may survive though progressively disabled for longer periods

Treatment No treatment is known to influence the course of the disease though vigorous anticonvulsant therapy may be required for the control of seizures

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258 NUTRITIONAL DISORDERS OF THE NERVOUS SYSTEM

Maurice Victor and Raymond D Adams

The modern concept of nutritional disease is of relatively recent development Although the clin

lateral optic neuritis without signs of cord damage may be abortive examples of this syndrome and the same may well be true of a proportion of cases of transverse myelitis

Cerebrospinal fluid changes are not distinctive the fluid may occasionally be normal but more often shows a moderate increase in protein and mononuclear cells

Diagnosis The relationship of this syndrome to disseminated encephalomyelitis and multiple sclerosis has already been mentioned the main reasons for considering it separately are that visual loss is rare in the former and not often bilateral in the latter In cases with optic disk swelling intracranial tumor may be considered in differential diagnosis but this problem will rarely present serious difficulty similarly distinction from optic neuritis of diverse etiology will usually be straightforward since in the latter condition it is general for only one eye to be affected In cases without spinal cord involvement temporal arteritis may come to mind as a possible cause of visual loss but it affects a different age group and the appearance of the temporal arteries is characteristic In other cases the distinction from syphilitic meningomyelitis or cord tumor will generally be made with ease by spinal fluid examination

Prognosis About half the cases die usually from intercurrent infection but the others may recover to a remarkable extent some apparently completely A significant number are left with permanent severe visual loss and paraplegia

Treatment There is no specific therapy for this condition treatment must be directed to palliation of pain and other symptoms and as in any case of paraplegia meticulous nursing care is required

DIFFUSE CEREBRAL SCLEROSIS

In 1912 Schilder first called attention to a disease in which progressive massive demyelination of the white matter of the cerebral hemispheres occurred and the condition was later referred to as *Schilder s disease* or *encephalitis periaxialis diffusa* Since that time many other cases have been described some resembling Schilder s original description others differing in certain specific details An attempt has been made by Krabbe Pelizaeus Merzbacher and others to define certain clinical subgroups on the basis of variations in age of onset familial incidence and clinical course Three broad pathologic types have been distinguished one corresponding to Schilder s original description and another showing changes which cannot be distinguished from those of cerebral multiple sclerosis The third type which has been reviewed in detail by Brain and Greenfield under the name *late infantile metachromatic leukoencephalopathy* is probably a separate disease entity and it may be that the cases of Krabbe and those of Pelizaeus and Merzbacher were in reality examples of this or still a fourth condition

Definition The *diffuse cerebral scleroses* are a group of conditions of unknown etiology some *occurring sporadically* others *running in families* which are characterized clinically by progressive visual failure mental deterioration and spastic paralysis and pathologically by massive demyelination of the white matter of the cerebral hemispheres

Pathology On inspection the brain often appears somewhat shrunken and feels firmer than usual but there are no other distinctive external appearances On section the white matter is seen to be largely replaced by a brownish gray rubbery translucent material which may occasionally show small cavities Usually the process spares the subcortical arcuate fibers thus giving a particularly distinctive appearance The changes are generally most advanced in the occipital lobes and involve the parietal and frontal areas to a variable extent but occasionally they may begin frontally the two hemispheres are often not affected symmetrically Balo has described certain cases in which demyelination occurs in concentric rings surrounding normal areas of white matter Adams and Kubik believe this appearance to be an occasional feature of multiple sclerosis but not of diffuse sclerosis

Histologic examination usually reveals that all myelin has disappeared from the affected areas and that axis cylinders have been involved to an almost equal extent In the older parts of the lesion there is proliferation of fibrous astrocytes but in the more recent areas swollen astrocytes are seen and around the margins of the lesion macrophages are plentiful The oligodendrocytes are almost completely destroyed Perivascular infiltration is minimal but in the vicinity of the more recent lesions the perivascular spaces may contain numerous fat filled macrophages

In the metachromatic form of diffuse sclerosis (Brain and Greenfield) the macroscopic appearances are similar though more symmetric but there is severe degeneration of the interfascicular oligodendroglia and large granular bodies staining metachromatically with thionine are frequent. This condition may well be a primary disorder of myelin development unlike the other demyelinating diseases

Clinical Manifestations In about half the cases the condition begins in the first decade Schilder s original description was of a disease occurring in early childhood but it is now recognized that this pathologic process may occur at any age More males than females suffer in childhood but in later years the sexes are equally affected

as well as *riboflavin* is probably essential for maintaining the integrity of peripheral nerves in some species

EXPERIMENTAL VITAMIN DEFICIENCY IN HUMAN BEINGS

The same method that has been successfully employed in assessing the role of *thiamine deficiency* in animals viz the use of a basal diet with the addition of all the crystalline vitamins except thiamine has been used in human beings Mental symptoms such as irritability depression defective memory and failure of concentration and peripheral symptoms such as parathesias and tenderness of the calves have been readily produced by this procedure The production of neurologic signs specifically those of polyneuropathy has been accomplished on only a few occasions after prolonged periods of deficiency

A different method has been employed in assessing the role of thiamine and other vitamins in the Wernicke Korsakoff syndrome The patients presenting neurologic signs were carefully evaluated over a period of several days while continuing to receive a diet completely lacking or deficient in the B vitamins Various vitamins were then added and the effect on the neurologic signs was noted It has been found that the addition of thiamine alone proved to have a dramatic effect in reversing the ophthalmoplegia as well as the drowsiness and apathy so characteristic of the acute stages of the disease the ataxia improved more slowly and frequently the nystagmus persisted indefinitely in less severe form The amnestic symptoms disappeared very slowly and incompletely and at times not at all

That *pyridoxine* is important in human nutrition was first suggested in 1951 when a large number of infants who were receiving a commercial milk product deficient in pyridoxine developed convulsive seizures Also it was discovered that the neuropathy which occurred in tuberculous patients receiving isonicotinic acid hydrazide (INH) was due to an interference or metabolic antagonism of pyridoxine Polyneuropathy as well as the characteristic skin changes of pellagra have been produced in human volunteers by the administration of a pyridoxine antagonist desoxypyridoxine Similarly abnormalities of the peripheral nervous system have been produced by using an antagonist of *pantothenic acid*

NUTRITIONAL DISEASES OF THE HUMAN NERVOUS SYSTEM

Except for subacute combined degeneration of the cord (vitamin B_{12} deficiency) and certain aspects of Wernicke s disease (vitamin B_1 deficiency) it is not possible to relate clinical syndromes to single vitamin deficiencies It would appear from experimental observations that polyneuropathy may result from one of several vitamin deficiencies Other syndromes such as beriberi which have been repeatedly ascribed to a deficiency of thiamine may be due to a deficiency of several factors This would be suspected where the diet consists mainly of milled rice The etiology of pellagra is even more complex as indicated in Chap 57 For these reasons a clinical classification is suggested comprising the following syndromes

1 Wernicke s disease and Korsakoff s psychosis
2 Nutritional polyneuropathy (neuritic beriberi)
3 Nutritional amblyopia (retrobulbar neuropathy)
4 Pellagra
5 Strachan s syndrome
6 Subacute combined degeneration of the cord

With the exception of subacute combined degeneration of the cord these syndromes are rarely seen in pure form instead there is considerable overlapping from one to another In patients with nutritional disease it is usual for more than one part of the nervous system to be involved this is a point of considerable diagnostic importance for involvement of both the central and peripheral nervous systems is found in only a few clinical circumstances Also the examination of these patients frequently discloses signs of malnutrition aside from those associated with the major neurologic syndrome These include general wasting various mucocutaneous lesions circulatory abnormalities and signs of scurvy

In this country the nutritional disorders of the nervous system are most often observed in the alcoholic population of the large urban centers Alcohol plays only a secondary role however mainly by displacing food in the diet It is also possible that excessive ingestion of alcohol impairs the absorption of nutrients and increases the need for thiamine by adding nonvitamin calories to the diet

Wernicke s Disease

In 1881 Carl Wernicke described an illness of sudden onset characterized by mental disturbance paralysis of eye movements and ataxic gait Swelling of the optic disks with retinal hemorrhages was also said to be present and in all three of his patients there was a progressive depression of the state of consciousness and death A fatal outcome was at one time regarded as a universal feature of this disease Wernicke described focal vascular lesions primarily affecting the gray matter around the third and fourth ventricles and aqueduct of Sylvius He regarded the disease as inflammatory

ical features of scurvy rickets pellagra and beri beri had been known for many years the idea that these illnesses resulted from a lack of essential foodstuffs was entertained for the first time only about the end of the last century Before then it was customary to ascribe disease to the deleterious effects of certain substances in the body i e toxins The suggestion that minute amounts of substances normally present in food could seriously influence the metabolic processes of the body was first clearly enunciated by Funk in 1911 He named these essential substances vitamines His work marked the beginning of the science of nutrition Since that time many vitamins have been isolated and synthesized and their relation to specific syndromes of disease has been demonstrated Also there have been advances in the over all aspects of nutrition—in the preparation storage canning and processing of food and more recently in its distribution to undernourished peoples These steps represent a great stride forward in man s economic and social development

As indicated in Chap 55 deficiency disease in man is not simply a matter of vitamin insufficiency Starvation a completely avitaminotic state is not attended by scurvy beriberi or pellagra Thiamine deficiencies are more likely to develop with diets *high in carbohydrate It should* appear then that a certain amount of food is necessary for the development of these diseases Such factors as exercise growth pregnancy and illness in which there is an increased need for vitamins are influential in the production of an avitaminotic state Also lesions of the intestine and liver may interfere with absorption and synthesis and there is some evidence that the deficiency of one vitamin may be enhanced by the excess of another

Other factors appear to determine the peculiar selectivity of vitamin insufficiency For example during the Second World War Europeans and Canadians developed the so called "electric foot" syndrome whereas the natives of Hong Kong on the same diet almost all escaped this condition Moreover once electric foot had been contracted and recovered from a reexposure to dietary conditions which originally elicited the complaint no longer caused the symptoms to appear The significance of these observations is not clear Nor can it be adequately explained at present why similar deficiencies should cause such diverse syndromes as Wernicke s disease in one group of individuals and the syndromes of amblyopia and polyneuropathy in another

Finally it must be pointed out that there are foodstuffs other than vitamins which are of vital importance Certain amino acids are essential to normal nutrition as for example tryptophan in pellagra (see Chap 57) others probably are of importance although their exact place has not yet been determined

Of the known vitamins only the B group are of importance in diseases of the nervous system With the identification of the various members of this group a large number of experiments were undertaken to elucidate their specific role in the nutrition of the nervous system Most of this work has been done in animals but a considerable body of data has also accrued from experiments on man Conclusions drawn from the experimental work have been indiscriminately applied to human disease resulting in considerable confusion For the sake of clarity therefore the nutritional diseases of the nervous system will be considered from three points of view (1) the animal experimental diseases (2) the human experimental diseases and (3) the naturally occurring diseases in human beings

EXPERIMENTAL VITAMIN DEFICIENCY IN ANIMALS

Although much of the experimental work is open to serious criticism there is a body of experimental data in animals which clearly indicates that the B vitamins are essential in maintaining the integrity of the nervous system *Thiamine deficiency* in the *rat dog pigeon and chick may cause a degeneration* of peripheral nerves and where the dorsal roots or their ganglions are involved of the posterior columns of the spinal cord Lesions of the central nervous system in the region of the vestibular nuclei have been produced in the rat and in the pigeon In fox mink and cat similar lesions of the central nervous system have resulted from the use of a fish diet containing a thiamine destroying enzyme thiaminase These lesions as well as those produced in monkeys by a thiamine deficient diet are similar in their topography and histologic character to those of Wernicke s disease

Pyridoxine deficiency has been found to be regularly attended by convulsions in a large number of species Swine and dogs in addition suffer an ataxia of gait and weakness of the limbs In these animals degenerative changes have been observed in the peripheral nerves dorsal root ganglions the posterior roots and the posterior columns of the spinal cord These findings would explain the weakness and ataxia but in the brains no abnormalities have been found In pyridoxine deficient monkeys abnormalities have been observed in the large nerve cells of the cerebral cortex, consisting of swelling eccentricity of the nuclei and loss of the Nissl particles This cell change bears a strong resemblance to that seen in human pellagra

A deficiency of *pantothenic acid* like that of pyridoxine causes a degenerative change in the peripheral sensory neurones of swine This vitamin

ever indications of disordered cardiovascular function in these patients such as tachycardia exertional dyspnea postural hypotension and minor electrocardiographic abnormalities Occasionally the patient may die suddenly the mode of death suggesting cardiovascular collapse It has been shown that Wernicke s disease is characterized by a state of high cardiac output out of proportion to the oxygen consumption The authors own observations suggest that this is because of an abnormal state of vasodilatation which in turn may be related specifically to thiamine deficiency

Pathologic Changes Views on the pathology of this disease have altered considerably since Wernicke s time It is now known that the disease process is limited neither to gray matter nor to the upper brain stem Hemorrhagic lesions as the original name suggested are not present in all instances and when they are do not necessarily represent the most significant or prominent change Post mortem examination reveals symmetrically located lesions in the paraventricular regions of the thalamus and hypothalamus the mammillary bodies the periaqueductal region of the midbrain and the floor of the fourth ventricle particularly in the region of the dorsal motor nucleus of the vagus The lesions are invariably found in the mammillary bodies and less consistently in the other areas Microscopically the principal change consists of varying degrees of necrosis of parenchymal structures There are a vacuolization of the tissue and a looseness of structure some nerve cells are lost but many are left either in a damaged or normal state Many nerve cells and fibers are destroyed others remain intact and are seen against a background of reactive glial elements both astrocytes and microgliacytes The blood vessels are prominent owing to adventitial and endothelial proliferation Hemorrhages are discrete and usually give the appearance of being of recent origin These microscopic changes are most intense in the center of the lesion shading off towards the periphery where there are some looseness of structure and proliferation of microglial cells and where some nerve cells appear shrunken and eosinophilic All the oculomotor nuclei either are spared entirely or are involved only to a mild degree and the same is true of the medial longitudinal fasciculi which connect them The lack of significant structural changes in these nuclei is consistent with the rapid clinical improvement in oculomotor function Several of the authors cases have also shown cerebellar lesions consisting mainly of a loss of Purkinje cells with the vermis more affected than other parts and the superior vermis more affected than the inferior The cerebellar lesions require further study

Etiology Wernicke s syndrome is no longer regarded as inflammatory in nature or as the result of the neurotoxic effects of alcohol Nutritional deficiency is now established as the causal factor Outbreaks have been encountered in prisoner of war camps and occasional cases have been reported in wasting diseases of varied origin where alcohol played no part The specific nutritional factor in most if not all the symptomatology of Wernicke s disease is thiamine The experimental evidence for this statement both in animals and in man has been mentioned This idea has received confirmation through numerous clinical observations The marked sensitivity of the ophthalmoplegia to the administration of thiamine accounts for the rapid disappearance of this sign following the ingestion of one or two meals The quality of prompt reversibility suggests that these symptoms are due to a biochemical abnormality and not to structural change On the other hand the memory loss responds slowly or not at all suggesting that this symptom is the result of structural changes presumably in the mammillary bodies and adjacent areas in the walls of the third ventricle

Korsakoff's Psychosis

Korsakoff s psychosis is generally defined as a state of memory defect with confabulation These features alone however fail to characterize this disease adequately It was apparent from Korsakoff s writings that his patients displayed a much wider range of symptoms including those of delirium and what he termed irritable weakness" (anxiety fear and depression) Furthermore if one subjects these patients to formal psychologic testing they are found defective in concentration verbal and visual abstraction visual motor coordination and learning ability Although such a pattern is probably not specific for Korsakoff s psychosis it is worth emphasizing that there are in this disease a number of abnormalities in cognitive function apart from those of memory defect Nevertheless as has been repeatedly stressed memory is disturbed out of proportion to other cognitive functions Thus a patient may be capable of performing adequately the problems posed by a standard intelligence test and yet within a few minutes of completing the test be unable to recall either the examiner or having taken the test Although it is recent memory that suffers most this is a relative matter the memory of events preceding the illness is always defective and even remote memory may be defective in severe cases

Of the various abnormalities of memory function two seem to be of particular importance (1) a persistent inability to learn newly presented material i e to make new memories and (2) an inability to recollect past events in their correct temporal sequence The inability to learn newly presented material is quite as distinctive of Korsakoff s psy

in nature and suggested the name *acute superior hemorrhagic polioencephalitis*

Since Wernicke s time views regarding this disease have undergone considerable modification clinically pathologically and etiologically

Symptoms and Signs The crux of the clinical picture is the ocular disturbance the diagnosis of Wernicke s disease at least during life cannot be made without it The usual ocular motor signs consist of (1) nystagmus both horizontal and vertical (2) paralysis of the external recti and (3) paralysis of conjugate gaze These signs show a considerable diversity The paralysis of conjugate movement varies from merely a nystagmus on extreme gaze in one direction to a complete loss of ocular movement in that direction Also vertical movements may be affected though abnormalities of the former are commoner Paralysis of downward gaze is an unusual manifestation of Wernicke s or in fact of any neuroophthalmic disease Next to nystagmus one most frequently encounters a lateral rectus muscle weakness or paralysis The sixth nerve palsy is always bilateral though not always symmetric and is accompanied by diplopia and internal strabismus With lateral rectus paralysis there may be an initial absence of nystagmus in the abducting eye the nystagmus becoming evident as the weakness improves In advanced stages of the disease there may be a complete loss of ocular movement and the pupils which ordinarily are spared may become miotic and non reacting Other ocular disturbances such as ptosis retrobulbar neuropathy retinal hemorrhages involvement of the near far focusing mechanism and internuclear ophthalmoplegia are decidedly rare although they do occur on occasion The authors have never observed papilledema in this disease

The ataxia is mainly one of stance and gait In its severest form the patient is literally unable to stand or walk without support The mildest degree of ataxia may be brought out only by special tests such as heel to toe walking In contrast to the gross disorder of locomotion is the relative infrequency of a clear cut intention tremor When present it is more likely to be encountered on heel to shin than on finger to nose testing Scanning speech is present only in isolated instances The ataxia of gait is most likely cerebellar in origin *but it is often* mistakenly attributed to a polyneuropathy

Affection of the peripheral nerves is common in Wernicke s disease occurring in over half the patients in the majority of these patients however the signs of neuropathy are so slight that they could not account for the disordered gait Nevertheless in a small proportion the neuropathy is so severe that stance and gait cannot be tested

The third consistent clinical feature of Wernicke s disease is the mental disturbance Several distinct groups of mental symptoms can be recognized as follows

1 The characteristic mental symptoms of delirium tremens or its variants i e hallucinations and other disorders of sense perception confusion agitation and autonomic overactivity The symptoms *are evanescent in nature and may clear with* out any treatment

2 A mental disorder the outstanding feature of which is apathy listlessness and severe confusion Unconsciousness as part of the initial episode is distinctly rare and also drowsiness is not common Instead the patient s mental state is better described as one of lack of interest or indifference His spontaneous speech is minimal and he is inattentive and cannot concentrate on the simplest task Many questions directed to him go unanswered or he may suspend conversation in the middle of a sentence to turn over and sleep He is readily roused from this state however What questions the patient answers betray disorientation in time and place misidentification of those around him and an inability to grasp the meaning of his illness or immediate situation Many of his remarks are irrational and show no consistency from one moment to another Under these circumstances a proper evaluation of the mental status is seldom possible When the patient s interest and attention can be maintained for a long enough period to ensure adequate testing one usually finds an impairment of retentive memory and of other cognitive functions If these patients are given thiamine or simply an adequate diet they lose most of these symptoms in a matter of days They become more alert attentive and responsive and in general more able to take part in mental testing At this time it becomes evident that the most prominent abnormality is one of retentive memory or what is ordinarily regarded as Korsakoff's psychosis

3 The characteristic disorder of retentive memory and of other cognitive functions that is recognized as Korsakoff's psychosis

The symptoms may have an acute onset and all of them may appear at the same time More frequently however the ophthalmoplegia and ataxia precede the mental signs by a few days or a week Unlike the patients described by Wernicke all of whom *died a lethal termination is not invariable* Only 16 per cent of the authors patients died and they had an illness complicated by other serious diseases such as cirrhosis of the liver or tuberculosis These patients may also show other stigmas of malnutrition the most frequent of which is polyneuropathy Occasionally amblyopia or spinal spastic ataxia may be added to the clinical picture

Although neuropathy is commonplace in Wernicke s disease the advanced stages of beriberi heart disease are rarely observed There are how

troublesome they consist mainly of numbness prickly feelings coldness deadness tenderness of the calf and plantar musculature or unusual sensitivity to contact In a minority of patients pain and paresthesias constitute the chief complaints The pain may take the form of a dull constant ache in the feet sometimes of the entire leg often the *pains are sharp and lancinating momentary in* duration quite like the lightning pains of tabes dorsalis Complaints of coldness are common but they are purely subjective the feet feeling quite warm to touch Much more distressing and incapacitating are the "burning" feelings and sensations of heat usually these affect the soles and less frequently the dorsal aspects of the feet as well They fluctuate in intensity or may be clearly intermittent in nature Characteristically a patient afflicted with pains and paresthesias suffers not one but all of the symptoms enumerated Although the painful symptoms may arise spontaneously they are made much worse by any contact with the feet The amount of pressure required to produce discomfort varies in severe cases the patient cannot bear to have the bedclothes touch his feet or to have the cold metal of an eating utensil touch his hands Because of these dysethesias he may be unable or unwilling to walk despite the preservation of motor power

The examination reveals varying degrees of motor *reflex* and *sensory loss* As the symptoms would suggest the signs are symmetric usually more prominent in the distal portions of the limbs and often confined to the legs The weakness varies greatly in degree It may be evident only with muscular exertion or it may take the form of a foot and wrist drop or even of a complete paralysis of the limb The deep reflexes in the legs are almost universally lost even with the mildest degrees of weakness and this is also true in the arms although occasionally the tendon reflexes are retained here despite serious loss of power in the hands In a small number of patients particularly those with pain and paresthesias the reflexes may be of greater than average briskness The sensory loss usually involves all the modalities Although one cannot adequately equate touch pain and temperature and vibratory and position sense some patients seemingly show an impairment or loss of one modality out of proportion to the others There is no sharp border between normal and impaired sensation the sensory loss which is most profound distally shades off gradually the transition to normal sensation *occurring over a long vertical extent* of the limb

As a rule only the limbs are affected and the abdominal thoracic and bulbar musculature are intact In some instances of Oriental beriberi, sensory loss has reportedly involved the face and abdomen as well Tinnitus vertigo nerve deafness aphonia due to vocal cord paralysis (particularly in infants) and retrobulbar neuropathy may also complicate beriberi in rare instances The relation of these disturbances to beriberi has been a point of contention that cannot be settled with finality since the specific cause of neither is known Far *more frequently they are engrafted on the syn*drome of ataxia and burning tender feet and are therefore appropriately considered as a part of Strachan's syndrome

The *spinal fluid* in the nutritional neuropathies is usually normal although an occasional case may show a slight elevation of the protein content The normal spinal fluid may be helpful in distinguishing the rapidly evolving form of nutritional neuropathy from infectious polyneuritis

Recovery is invariably a slow process In the mildest cases there may be considerable restoration of motor power in a few weeks in the severest forms several weeks may pass before even the first signs of recovery become manifest and up to a year before the patient is able to walk unaided Recovery in severely affected patients is often incomplete and they may be left with some weakness of the feet and an absence of the knee and ankle jerks The development of contractures due to inadequate physiotherapy prolongs convalescence

Pathologic Changes *Pathologically* nutritional neuropathy is characterized by a degeneration of the peripheral nerves and in advanced cases of the anterior and posterior nerve roots The degenerative process is more intense in the distal segments than in the proximal ones Both the myelin and the axis cylinders are destroyed the former probably earlier and to a greater extent than the latter The degeneration is Wallerian in type in some places whereas in others there may be segments of nerve in which the myelin is lost and the bare axis cylinders remain (the segmental demyelination of Gombault) Dorsal root ganglion cells may be lost to variable extent and the anterior horn cells of the spinal cord show an axonal reaction The latter change is probably secondary to the axis cylinder damage in the anterior roots and peripheral nerves

The "Burning Feet" Syndrome The term *burning feet* is frequently applied to a state in which pain in the extremities is the outstanding symptom and in which the advanced signs of neuropathy may be absent It is doubtful whether this syndrome merits *classification apart from other nutritional neuropa*thies it is here considered separately out of deference to the many reports from the prisoner-of war and internment camps of the Far East In these reports the pain is variously described as tingling burning aching shooting cramplike or

chosis as is the disorganization of past memory Since the adaptation to every new situation requires the forming of new memories or at least combining new and old ones it is the defect in this function which renders the patient helpless in society and capable of performing only the most routine tasks Moreover when the patient attempts to reconstruct the past there are large gaps in the recounted material Only isolated facts are retained and these are not combined in proper chronology so that the whole is distorted Or new material may be introduced drawn from the patient s own experience and having some logical relation to the story This defect becomes obvious after the acute stage of the illness has passed and some improvement in function has occurred, and it remains the dominant disturbance in all but the few patients who make a complete recovery

In addition to the disorders of cognitive function and memory a significant proportion of patients show a *state of confusion* particularly in the early stages of their illness Such patients are quite unable to grasp their immediate situation—to recognize the examiner as a physician to appreciate that they are in the hospital the time of the day or season of the year etc They misidentify people around them and misinterpret their actions and apprehension and at times even panic may be aroused by their misinterpretations and delusions In such states as in delirium the confusion appears to depend not so much on amnesia as on a widespread perceptual disorder

Confabulation is widely regarded as a specific symptom of Korsakoff's psychosis but this is not true for it is found in many other confusional states as well Furthermore confabulation is not observed in all the patients with Korsakoff s psychosis and the diagnosis can readily be made without it

The outcome of Korsakoff s psychosis varies In a small proportion of patients complete recovery may be expected More commonly there is slow and incomplete recovery over a year or longer Depending on the severity of the residual symptoms the patient may or may not be able to lead an independent existence out of a hospital If the damage to the brain is severe permanent commitment to a psychiatric hospital is required The residual mental state is usually one in which the patient shows large gaps in memory and the inability to sort out events in their proper temporal sequence If the patient is seen for the first time during this stage the diagnosis of alcoholic deteriorated state" or organic brain syndrome due to alcohol is commonly made

The Unity of Wernicke s Encephalopathy and Korsakoff's Psychosis Several allusions have already been made to the relation between these two syndromes Clinically the majority of patients with Wernicke s disease show signs of Korsakoff's psychosis either from the time they are first seen or following a period of apathy and drowsiness Conversely the vast majority of patients with an amnestic confabulatory psychosis show the stigmas of Wernicke s disease (slight nystagmus and ataxia) even years after the onset of the illness The pathologic changes in the brain are very much the same whether the patient dies in the acute stages of Wernicke s disease or in the chronic phase of the illness when the ocular palsies have cleared and the amnestic symptoms predominate It would appear that in the nutritionally deficient alcoholic patient Wernicke s disease and Korsakoff s psychosis represent but different facets of the same disease process

Nutritional Polyneuropathy (Neuritic Beriberi)

For many years this was believed to be an exclusively Oriental disease After the First World War and particularly in the last two decades it became established that there was no essential difference clinically or pathologically between the neuropathy of beriberi and that which occurred among alcoholics in the Western Hemisphere Even the cardiovascular manifestations of beriberi have their counterpart in the alcoholic populations For these reasons alcoholic (nutritional) neuropathy and dry (neuritic) beriberi will be treated together

Symptoms and Signs The symptomatology of nutritional polyneuropathy is remarkably diverse In fact many patients are asymptomatic Only upon careful examination will the thinness of the leg muscles and loss or depression of the knee and ankle jerks or of the ankle jerks alone be detected Less frequently calf tenderness somewhat diminished muscle power in the feet and legs or a patchy blunting of pain and touch sensation over the feet and shins are also found

Patients with the manifest form of alcoholic beriberi report a variety of symptoms consisting of weakness paresthesias and sometimes pain The symptoms are usually insidious and slowly progressive although at times there may be a rapid progression in the weakness In a small but characteristic group the transition from an asymptomatic state to one of virtual paralysis occurs in a matter of several days The symptoms are at first referred to the distal portions of the limbs and progress proximally if the illness remains untreated The legs are affected earlier than the arms these are the only members of the body which are involved Only in exceptional cases may the arms be affected more severely than the legs Motor and sensory symptoms usually occur concomitantly although the patient may complain much more of one than the other Usually weakness constitutes the source of disability Sensory symptoms may however be

an acute confusional psychosis dominates the clinical picture Pellagra not only may produce insanity but occasionally may result from it because of the anorexia and refusal of food that accompany certain mental illnesses The manifestations of spinal cord involvement have not been clearly delineated perhaps because the mental state of the patients has precluded accurate testing In general they are referable to both the peripheral nerve and posterior columns as well as the lateral column predominantly the former Neuritic signs are often difficult to distinguish from affection of the posterior columns Signs such as tremors extrapyramidal rigidity sucking and grasping reflexes and coma have been ascribed to the pellagrous syndrome as have various disorders of the special senses

The distinctive *pathologic changes* in pellagra are most readily discerned in the large cells of the motor cortex, the cells of Betz which appear swollen and rounded with eccentric nuclei and loss of the Nissl particles This change was first described by Adolf Meyer as *central neuritis* and is frequently referred to as *axonal reaction* because of the similar nerve cell change which occurs most frequently in the anterior horn cells when their axones are severed It is likely that the central neuritis of pellagra is not dependent on injury to the axones of the Betz cells Rather it appears to represent a primary affection of the whole motor cell The spinal cord lesions take the form of a symmetric degeneration of the dorsal columns especially of Goll, and to a lesser extent of the pyramidal tracts The posterior column degeneration affects a specific system of fibers and is secondary to the degeneration of the posterior roots The nature of the pyramidal tract lesion in pellagra is not known one can only speculate that this change is secondary to the pyramidal cell degeneration

A spinal spastic syndrome apart from the other symptoms and signs of pellagra, may be a rare manifestation of deficiency disease The chief clinical signs are spastic weakness of the legs with absent abdominal and increased tendon reflexes clonus and extensor plantar responses These signs are usually accompanied by other signs of nutritional deficiency such as Wernicke s disease delirium and retrobulbar and peripheral neuropathy

Strachan s Syndrome

Beginning with the report of Strachan in 1888 and culminating with the recent observations among prisoners of war and civilian internees there has appeared a large number of reports about a condition which cannot be forced into the boundaries of the classical nutritional syndromes of Wernicke Korsakoff beriberi pellagra or pernicious anemia and subacute degeneration of the spinal cord When these descriptions are viewed collectively a symptom complex emerges the principal features of which are paresthesias of the feet hands trunk and even face burning tender feet impaired vision and loss of reflexes Less common features are dizziness deafness hoarseness acute myasthenia spasticity and mucocutaneous lesions Strachan was the first to describe this syndrome although he did not recognize its nutritional etiology

Strachan s syndrome is essentially a disorder of the peripheral and optic nerves Clinically sensory symptoms and signs dominate the picture in this respect the syndrome differs from beriberi Paresthesias of the extremities face and trunk painful hyperesthesia" of the feet loss of superficial and deep sensation and ataxia are the common manifestations On the other hand foot drop and muscle weakness occur very rarely A frequent associated disorder is failing vision, which may go on to complete blindness and pallor of the optic disks In general deafness and vertigo are rare complications but in some outbreaks these symptoms were so common as to earn the epithet "camp dizziness" Along with the neurologic signs there are varying degrees of stomatoglossitis corneal degeneration and genital dermatitis these mucocutaneous lesions are often spoken of together as the *orogenital syndrome* and are quite distinct from those of pellagra

There have been only a few pathologic studies of this syndrome Aside from the damage to the papillomacular bundle in the optic nerve the most consistent abnormality has been a loss of medullated fibers in each column of Goll adjacent to the midline This indicates a systematized degeneration of the central process of the bipolar sensory neurone of the lumbosacral spinal ganglions The fact that the primary sensory neurone is the chief site of disease is consistent with the predominant sensory symptomatology

Subacute Combined Degeneration of the Spinal Cord and Brain

Subacute combined degeneration of the spinal cord the neurologic component of pernicious anemia is due to a vitamin deficiency (vitamin B_{12}) but is clearly different from the other nutritional diseases The disease results not from the lack of vitamin B_{1} in the food but from the inability to transfer minute amounts of the vitamin across the intestinal mucosa apparently the result of a failure of gastric secretion Such "starvation in the midst of plenty" has been called *conditioned deficiency disease* The general features of pernicious anemia are fully discussed in Chap 212 here only the neurologic manifestations will be considered

Clinical Manifestations Symptoms of nervous system disease are present in 75 to 89 per cent of patients with pernicious anemia The patient first

resembling the lightning pains of tabes The pain was often very severe it was greatest at night and interfered with sleep Some patients found relief from the application of cold others only in movement The presence of associated neuritic signs was a variable matter In some patients wasting dropped foot reflex loss and sensory changes were completely wanting in a significant proportion the tendon reflexes were exaggerated but without clonus or extensor plantar responses However in other groups of patients the painful feet were but one stage in the evolution of a peripheral neuropathy characterized by tenderness of the calves reflex and sensory loss and ataxia and complicated in many cases by retrobulbar neuropathy

In alcoholic (nutritional) polyneuropathy pain is the outstanding symptom in a small group of patients however they do not constitute a distinct group in terms of their neurologic signs Pain and dysesthesia may be a prominent symptom in cases with all degrees of motor reflex and sensory loss In some cases the weakness may be slight or absent and in rare instances reflexes may be retained despite a severe "burning feet syndrome However in all cases of severe hyperesthesia even where the slightest stimulus appears intolerable there is usually sensory loss one is able by using finely graded stimuli to demonstrate an elevated threshold to painful thermal and tactile stimuli in the hyperesthetic zone The term *hyperesthetic* is therefore not well chosen it implies a heightened receptiveness of the nervous system or an increased response of the receptors to tactile and painful stimuli Actually there is an underlying sensory deficit or an elevated threshold to various stimuli once the stimulus is perceived however it may have a severely painful or unpleasant quality (hyperpathia)

Obviously the term *burning* is not particularly applicable considering the wide variety of symptoms apart from thermal dysesthesias Because of this as well as the fact that the hands may be involved the term *acrodysesthesias* or *painful extremities* is preferred by some

Although undoubtedly nutritional the specific deficiency responsible for the dysesthesias has not been clearly established The pathophysiology is likewise unknown Spillane suggests that this affection is an early stage of nutritional disturbance in the nerves to the lower limbs He draws an analogy to the burning pains produced by the interruption of conduction in large nerve fibers by rendering a limb ischemic The authors have been impressed by the similarity of the pain to causalgia and in several patients have succeeded in abolishing the pain for several hours to days by paravertebral sympathetic block These observations require confirmation

Nutritional Amblyopia

This term refers to the visual failure which occurs in nutritional disease but which is not due to a lesion of the cornea or other parts of the eye concerned with refraction The site of the lesion is most likely in the optic nerve so that the term *retrobulbar neuropathy* is a suitable synonym

Clinically the characteristic symptom is a blurring of vision for near and distant objects usually developing gradually over a period of several weeks Examination discloses a reduction in visual acuity the presence of central and centrocecal scotomas for white or colors and in some cases fundoscopic abnormalities The latter vary from a mild papillitis slight hyperemia and perhaps blurring of the disk margins to pallor of the optic disk in the most advanced cases Retinal hemorrhages may be seen occasionally These changes are always bilateral though frequently asymmetric Untreated the disease may progress to irreversible optic atrophy With nutritious diet and multiple vitamin supplements improvement occurs in all instances though to a variable extent

In this country many if not all of the cases of retrobulbar neuropathy attributed to the toxic effects of alcohol or tobacco are probably of nutritional origin Retrobulbar neuropathy may occur as the only manifestation of deficiency but far more frequently it is combined with other nutritional syndromes such as peripheral neuropathy the Wernicke Korsakoff syndrome or rarely by a spinal spastic and ataxic syndrome (Strachan s disease)

Deficiency amblyopia was particularly prevalent during the last war in the prisoner of war and civilian internment camps of the Far East Although it had previously been described in association with beriberi and pellagra the peak incidence did not coincide with that of either of these syndromes but with the mucocutaneous lesions in orogenital regions and burning feet syndromes Although the amblyopia seemed to respond best to a diet rich in riboflavin the etiologic relationship to this vitamin cannot be regarded as established

Pellagra

This discussion is concerned only with the neurologic manifestations which in themselves are extremely diverse Pellagra is essentially an encephalopathy although involvement of all parts of the nervous system has been described In the early stages of the disease the symptoms are mainly mental and may be mistaken for those of a psychoneurosis Insomnia fatigue nervousness irritability or feelings of depression are common complaints Examination may reveal retardation of mental processes and impairment of memory Sometimes

vitamin B_{12} daily is an adequate dosage in the treatment of subacute combined degeneration of the cord but in practice the amount prescribed is usually higher

The improvement in neurologic signs is quite dramatic and complete when effective therapy is instituted early after the onset of symptoms In practically all instances at least partial improvement is effected although in long standing cases often the best that can be accomplished is arrest of progression The most important factor influencing the response to treatment is the duration of the disease as measured by the duration of difficulty in walking The greatest improvement occurs in those whose difficulty in walking is of less than 3 months duration and conversely the least improvement occurs in those with difficulty in walking of longer than 2 years duration Factors of little or no importance are age sex severity arteriosclerosis hypertension and the degree of anemia Neurologic relapses during therapy are usually associated with infections and can be corrected by increasing the dose of liver extract or vitamin B_{12} All neurologic symptoms and signs may be improved extensor plantar responses are as responsive to treatment as paresthesias and loss of vibratory sense The return of absent deep reflexes is commonly observed although at times it may take longer than a year Most improvement occurs during the first 3 to 6 months of therapy but there may be continued improvement for a year or longer

Diagnosis The chief obstacle in the early diagnosis of subacute combined degeneration of the cord is the lack of parallelism between the hematologic and neurologic manifestations With the widespread use of folic acid this problem has become more acute since this drug may cause a hematologic remission for an indefinite period while the neurologic signs worsen often to an irreversible stage Other problems concern the difficulty of distinguishing between intrinsic spinal cord disease of non pernicious anemia type from posterior and lateral column disease due to pernicious anemia and of distinguishing pernicious anemia and subacute combined degeneration from other macrocytic anemias and their associated neurologic disturbances

In most instances the diagnosis can be made by utilizing the standard methods for the diagnosis of pernicious anemia (see Chap 212) the examination of the blood gastric acidity and the bone marrow These methods are of limited value when the anemia is mild or absent or when the anemia has been corrected by folic acid A therapeutic trial of vitamin B_{12} may be employed but recourse to such a procedure means that therapy must be continued indefinitely and the diagnosis may remain in doubt Under these circumstances a number of refined diagnostic aids may be employed such as the Schilling test (Chap 212) or the microbiologic assay of B_{12} utilizing the organism *Euglena gracilis*

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259 DEGENERATIVE DISEASES OF THE NERVOUS SYSTEM

Edward P Richardson Jr

The term *degenerative* as applied to diseases of the nervous system is used to designate a group of disorders in which there is gradual generally symmetric relentlessly progressive wasting away of structural elements of the nervous system for reasons still unknown Many of the conditions so designated clearly depend upon abnormal genetic factors and thus appear in more than one member of the same family this general group of diseases is therefore frequently referred to as *heredodegenerative* A number of others without apparently differing in any fundamental way from the hereditary group occur only sporadically i e as isolated instances in a given family It is obvious that to call these diseases degenerative is to say that the underlying causes are as yet undetermined Sir William Gowers in 1902 suggested the now familiar term *abiotrophy* to describe them by which he meant that diseases of this class were based upon defective vital endurance of the affected parts which led to their premature death Concise and convenient as this term may be it of course tells little or nothing of the true nature of the defects It is to be assumed that the basis for these diseases must be found in *some* disorder of the metabolism of the parts involved

Within relatively recent times there has been some elucidation of the nature of a number of nervous disorders which in their symmetric distribution and graduallly progressive course resemble the class of diseases under discussion Examples of these are the deficiency diseases such as subacute com

notices general weakness and paresthesias consisting of tingling pins and needles feelings or other vaguely described sensations The paresthesias tend to be constant to progress steadily and to be the source of much distress They are localized to the distal parts of all four limbs in a symmetric distribution the lower extremities usually being involved before the upper ones As the illness progresses stiffness and weakness of the limbs develop especially of the legs and combined with a defect in postural sensation produce a weak unsteady gait and awkwardness of the limbs If the disease remains untreated an ataxic paraplegia with variable degrees of spasticity and contracture may develop

Early in the course of the illness when only paresthesias are present there may be no objective signs Later the neurologic examination may indicate a disturbance of all parts of the nervous system but mainly of the posterior and lateral columns of the spinal cord Loss of vibration sense is by far the most consistent sign it is more pronounced in the legs than in the arms and frequently it extends over the trunk Position sense is involved somewhat less frequently Isolated instances of loss of superficial sensation below a segmental level on the trunk do occur implicating the spinothalamic tracts but such a finding should always suggest the possibility of some other disease of the spinal cord More commonly the defect of cutaneous sensation takes the form of a mild blunting of touch pain and temperature sensation over the limbs in a distal distribution

Examination of the motor system discloses loss of power spasticity changes in the tendon reflexes clonus and extensor plantar responses These signs are practically limited to the legs At first the patellar and Achilles reflexes are found to be diminished in activity as frequently as they are increased and may even be absent With treatment the reflexes may return to normal or even become hyperactive Gait may be predominantly ataxic or spastic usually both The nervous system involvement in subacute combined degeneration is characteristically although not always symmetric A definite asymmetry of motor or sensory findings maintained over a period of weeks or months should always cast doubt on the diagnosis of subacute combined degeneration of the spinal cord

Mental signs are frequent ranging from irritability apathy somnolence suspiciousness and emotional instability to a marked confusional or depressive psychosis or intellectual deterioration Signs of visual impairment are distinctly rare when present they take the form of centrocecal scotomas If involvement of the optic nerve is severe optic atrophy may occur

Neuropathologic Changes The pathologic process takes the form of diffuse although uneven degeneration of the white matter There are multiple foci of spongy degeneration often in relation to small blood vessels The myelin sheaths and the axis cylinders are both affected the former perhaps earlier and to a greater extent than the latter There is relatively little fibrous gliosis in the early lesions but in the older ones so often seen in treated cases gliosis is pronounced The changes begin in the posterior columns of the thoracic cord and spread from this region up and down the cord as well as forward into the lateral columns The lesions are not limited to specific systems of fibers within the posterior and lateral funiculi but are scattered irregularly through the latter

The paresthesias impairment of vibratory and position sense ataxia and the Romberg sign are due to affection of posterior columns and lesions here may also account for loss of tendon reflexes Weakness spasticity increased tendon reflexes and Babinski signs depend on involvement of the pyramidal tracts in the lateral columns The spinothalamic tract may be involved in the pathologic process which explains the occasional clinical finding of loss of pain and temperature sensation at a segmental level on the trunk In advanced forms of the disease similar pathologic changes may occur in the white matter of the brain Instances of degenerative lesions of the optic nerves have also been verified at necropsy

There is no unanimity of opinion regarding the occurrence of lesions in the peripheral nerves in pernicious anemia The clinical evidence is stronger than the pathologic and the existence therefore of disease in the spinal roots and nerves is largely inferential It has been suggested that reversibility of neurologic signs is indicative of peripheral nerve involvement The distal and symmetric blunting to pain touch and temperature that occurs in many cases is certainly a point in favor of peripheral nerve disease It has been shown that there is a loss of myelin in peripheral nerves but there is no convincing evidence that axis cylinders are affected

Aside from the characteristic laboratory findings of pernicious anemia (see Chap 212) there are few laboratory tests that are specifically helpful in the diagnosis of the nervous system disorder The *spinal fluid* is usually normal although occasionally there may be a slight elevation of the protein content

Efficacy of Liver and Vitamin B_1 At first it was believed that the spinal cord and blood changes were due to separate deficiencies and for this reason treatment with liver extract was supplemented with crude liver However there is now sufficient evidence that the response to vitamin B_{12} alone is in all ways comparable to that from refined liver extract or crude liver It has been suggested that the equivalent of 1 μg of parenterally administered

A number of other examples could be cited (e g Friedreich s ataxia) in which certain related groups of neuronal systems disintegrate For this reason a number of the degenerative diseases have been designated as system diseases ("progressive cerebrospinal system atrophies"—Spatz) and their generally hereditary nature has been emphasized It must be realized however that disease processes of other kinds may likewise result in remarkably selective destructive effects as shown by the special vulnerability of the larger pyramidal cells of the hippocampus to hypoxia of the Purkinje cells of the cerebellum to hypoxia and hyperthermia and other similar examples On the other hand a number of other conditions can be cited in which classification with the degenerative group is fully justified and yet the disease process acts diffusely without restriction to particular systems—as for instance with Alzheimer s disease and the leukodystrophies Nonetheless with these reservations predominant affection of particular neuronal systems remains an important distinguishing feature

As a general rule it is the nervous system that is primarily affected and any disease process that may be found in other organs is secondary or unrelated Metabolic and biochemical investigations have failed to disclose any systemic disorder to which the neurologic changes can be attributed Since the pathologic process in the nervous system is one of slow involution of nerve cell bodies or their prolongations as nerve fibers without intense tissue reaction examination of the cerebrospinal fluid as would be expected shows at most a slight elevation of protein without abnormalities in pressure cell count or in other constituents Furthermore since these diseases result invariably in tissue loss rather than in new tissue formation (as with neoplastic or inflammatory conditions) x ray visualization of the ventricular system or subarachnoid space shows either no change or an enlargement of these compartments These negative laboratory findings thus help to distinguish the conditions under discussion from the other large classes of progressive disease of the nervous system—tumors and infections

CLASSIFICATION

Since etiologic classification is impossible the separation of the degenerative diseases into a number of syndromes rests on descriptive criteria based largely upon pathologic anatomy but to some extent on clinical aspects as well In the terms currently used to designate these morbid entities the names of a number of distinguished neurologists and neuropathologists are commemorated A useful way of keeping in mind the various disease states is to group them according to the outstanding clinical features that may be found in an actual case The following classification intended to be of practical help to the physician is based on such a plan

- I Conditions in which dementia is an outstanding feature in the absence of other striking neurologic signs
  - A Diffuse cerebral atrophy
    - 1 Senile dementia
    - 2 Alzheimer s disease
  - B Pick s disease (circumscribed cerebral atrophy)
- II Conditions in which dementia is strikingly combined with other neurologic signs
  - A Principally in adults
    - 1 Huntington s chorea
    - 2 Cerebrocerebellar degeneration
    - 3 Jakob Creutzfeldt disease
  - B In children and adults
    - 1 Amaurotic family idiocy (neuronal lipoidoses)
    - 2 Leukodystrophy
    - 3 Familial myoclonus epilepsy
    - 4 Hallervorden Spatz disease
    - 5 Wilson s hepatolenticular degeneration Westphal Strumpell pseudosclerosis
- III Conditions chiefly manifested by abnormalities of posture or involuntary movements
  - A Paralysis agitans (Parkinson s disease)
  - B Dystonia musculorum deformans (torsion dystonia)
- IV Conditions chiefly manifested by ataxia
  - A Cerebellar degenerations of late life
  - B Spinocerebellar degenerations (Friedreich s ataxia Marie s hereditary ataxia)
- V Conditions with outstanding muscular weakness and wasting
  - A Without sensory changes
    - 1 In adults
      - a Motor system disease
      - b Amyotrophic lateral sclerosis
      - c Progressive muscular atrophy
      - d Progressive bulbar palsy
      - e Primary lateral sclerosis
    - 2 In children or young adults
      - a Infantile muscular atrophy (Werdnig Hoffmann disease amyotonia congenita)
      - b Hereditary spastic paraplegia
  - B With sensory changes
    - 1 Syringomyelia (and syringobulbia)
    - 2 Progressive neural muscular atrophy
      - a Peroneal muscular atrophy (Charcot Marie Tooth)
      - b Hypertrophic interstitial neuropathy (Déjerine Sottas)
    - 3 Miscellaneous forms of chronic progressive neuropathy
- VI Conditions chiefly manifested by visual loss
  - A Hereditary optic atrophy (Leber)
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CONDITIONS IN WHICH DEMENTIA ALONE PREDOMINATES

In the disease entities about to be discussed the clinical picture is dominated by gradual loss of intellectual capacities i e by *dementia* Other neurologic abnormalities except in the terminal stages are absent or relatively insignificant (For further discussion of dementia including its clinical evaluation Chap 36 should be consulted)

Diffuse Cerebral Atrophy Senile Dementia, Alzheimer's Disease

Some degree of shrinkage in size and weight of the brain "atrophy" has been shown to be the inevitable accompaniment of advancing age In many instances this is of no clinical significance and there are many very old people who remain alert and perceptive with keen intellect to the end Nevertheless severe degrees of diffuse cerebral atrophy are always associated with some evidence of dementia When these changes occur in old age (and the definition of when old age begins is largely a subjective one) it is usual to speak of *senile dementia* That this is a fairly frequent condition is common experience Much more infrequent is a pathologically identical *progressive dementia* with diffuse brain atrophy coming on well before the senile period a *presenile dementia* This condition classically described in 1906 by Alois Alzheimer has since come to be generally known as *Alzheimer's disease* The distinction between the two conditions is purely a clinical one pathologically they differ only in that the characteristic abnormalities tend to be more severe and widespread in cases beginning at an earlier age than the senile period It is to be presumed that the basic underlying derangement is the same but that its effects differ somewhat depending on the age of the patient

Pathology The brain presents typically a generally shrunken appearance with atrophy of the convolutions and symmetric enlargement of the lateral and third ventricles Frequently these changes are especially pronounced in the frontal lobes Microscopically there is widespread loss of nerve cells most apparent in the cerebral cortex with secondary astrocytic glial proliferation In addition two types of lesions give this disease process its distinctive character (1) Scattered throughout the cerebral cortex are microscopic spherical deposits of amorphous material most easily seen with silver staining methods They are the so called senile plaques which have been known for some 65 years and which are generally considered to be an abnormal deposition or precipitation of material in the brain tissue rather than the remains of diseased nerve cells Despite numerous investigations and an extensive literature devoted to them their origin and nature still remain uncertain The other characteristic histopathologic feature is the *Alzheimer fibrillary change* in nerve cells This striking abnormality first clearly described by Alzheimer in his publication on presenile dementia consists of the presence within the cytoplasm of thick fiber like strands of silver staining material often in the form of loops coils or tangled masses This is a cytologic derangement which apparently ends in death of the cell for clumps of these fibrils can often be seen even after the cell bodies within which they arose have disappeared Despite ingenious attempts to explain them (cf von Braunmuhl 1957) the *true nature and meaning of these remarkable appearances have yet to be learned* Senile plaques and fibrillary changes occur most numerously in the cortex and are widely distributed although most frequent of all in the frontal lobes and hippocampal gyri They have been encountered in all regions of the brain but rarely if ever in the spinal cord Abundant pathologic evidence clearly establishes that the *neuropathologic alterations just described* are not related to vascular disease or to any known systemic disorder

Clinical Aspects This condition has been described as occurring during every age period even in childhood although it is most frequently a disease of the later decades of life Although a number of well-documented familial cases exist there is not sufficient evidence to indicate that this is truly an hereditary disorder in practice most cases are seen as sporadic instances The onset is insidious and subtle with changes first most noticeable in the faculties of memory for recent happenings and for over all judgment of situations Emotional disturbances such as depression or anxiety states or odd unpredictable quirks of behavior may be salient features in the early stages Progression is very slow and gradual and unless the condition is earlier brought to a close by the effects of advanced age it may linger on for some 10 to 15 years

In the milder cases including those of the senile period the noteworthy features are those of simple dementia as described in Chap 36 More atypical disorders of thought and intellect including aphasia apraxia like disturbances and abnormalities of space perception may be encountered in the more severe forms such as are seen in younger individuals Neurologic examination characteristically discloses no other abnormalities Additional investigative procedures including the usual blood and cerebrospinal fluid determinations and electroencephalography do not yield any conclusive or pertinent data The enlargement of the ventricular system and subarachnoid space resulting from the diffuse brain atrophy can be demonstrated by pneumoencephalography

otherwise no characteristic roentgenographic findings are seen During the course of the illness occasional convulsive seizures may occur but they do not always accompany the disorder Terminally a state of total helplessness is reached and the patient dies from intercurrent disease Usually long before the end institutional care is necessary

Differential Diagnosis The diagnosis is made by excluding by means of the usual clinical methods other conditions that may produce dementia The concern of the physician must naturally be to make certain that there is no condition which may improve with treatment such as tumor chronic subdural hematoma infection (e g syphilitic or tuberculous meningoencephalitis) or well defined metabolic or deficiency disease Ordinarily the clinical picture of very gradually progressive dementia without definite focal neurologic signs without evidence of increased intracranial pressure pleocytosis or significantly raised protein in the cerebrospinal fluid in the presence of otherwise good general health is in itself sufficient to lead unmistakably to the diagnosis of a diffuse degenerative disease of the brain which is almost always of the type under discussion In the presence of such evidence it should not be necessary to resort to more complicated procedures to make this diagnosis However it is usual since so much depends on it to ensure the accuracy of the diagnosis by pneumoencephalography

Pick's Disease (Circumscribed Cerebral Atrophy)

This remarkable form of cerebral atrophy was first brought to attention by a series of publications by Arnold Pick in Prague around the turn of the century In the differential diagnosis of dementia in the presenile period it is usually mentioned in the same breath with Alzheimer's disease however it is an extremely rare condition in comparison with diffuse cerebral atrophy of the Alzheimer type

Pathology So striking are the gross pathologic changes in the brain that in typical cases the diagnosis can be made at a glance One sees severe atrophy of the anterior portions of the frontal and temporal lobes and there is a curiously sharp line of demarcation between the atrophied portions and the remainder of the brain which appears normal or nearly so In some cases the frontal atrophy is more prominent in others the temporal lobes are more severely involved in general both regions are affected Not infrequently the process extends to the Rolandic and parietal regions but the occipital lobes invariably are spared In many of the reported cases the changes have been considerably more pronounced on one side of the brain than the other an exception to the general rule of symmetry in degenerative nervous disease but bilaterality is the rule Characteristically there likewise are atrophic changes in a number of subcortical structures caudate nucleus putamen thalamus and substantia nigra and in the descending frontopontine fiber system In the diseased regions there is local destruction of central and convolutional white matter out of proportion to the degree of loss of nerve cell bodies in corresponding areas of the cortex this finding has led to the supposition that it is the peripheral axonal processes of the nerve cells together with their myelin sheaths which atrophy first i e that there is a gradual dying back of the neurone from the periphery to the center A noteworthy histologic feature of this condition is the occurrence of numerous swollen "ballooned out" nerve cells in the atrophic regions a finding which has been interpreted as an axonal reaction or retrograde cell change secondary to the involutional process in the periphery Another frequently encountered cell change is the occurrence of spherical intracytoplasmic inclusions that stain deeply with silver impregnation methods the significance of this remains unexplained The peculiarly selective nature of the degenerative process in Pick's disease has led to its pathologic classification with the system diseases although not all observers adhere to this view The distribution of the brain atrophy does not correspond in any way with territories of vascular supply and it is to be presumed that the condition is totally unrelated to disorders of cerebral circulation

Clinical Aspects The differentiation during life between Alzheimer's and Pick's disease is difficult and is largely of academic importance Early dilapidation of personality with relative preservation of such intellectual faculties as memory and gross reasoning ability are considered to be particularly characteristic of Pick's disease also early involvement of areas related to language function in the posterior frontal and anterior temporal regions of the dominant cerebral hemisphere may lead to pronounced aphasia The disease is one of adult years especially of the presenile period (with onset at age fifty to sixty) A considerable number of cases with earlier onset have been reported (the youngest at twenty two) in these the condition tends to be somewhat more severe than in older individuals as in Alzheimer's disease Familial occurrence is on record in a number of instances Progression is slow and relentless with an average duration of about 7 years

Differential Diagnosis The considerations noted above with respect to Alzheimer's disease apply to Pick's disease as well The circumscribed frontotemporal atrophy can at times be demonstrated by pneumoencephalography

CONDITIONS COMBINING DEMENTIA WITH OTHER NEUROLOGIC SIGNS

Huntington s Chorea (Chronic Progressive Hereditary Chorea)

This condition which genetically follows the pattern of a mendelian dominant was classically described in 1872 by George Huntington who with his father and grandfather both physicians observed cases in members of a family living near his home in Long Island Unmistakable in its typical form the affliction combines progressive dementia with bizarre involuntary movements and odd postures Atypical cases have also been recognized (see below) but in general the disorder runs true to form

Pathology The brain has a generally atrophic appearance especially noticeable in the frontal lobes Particularly characteristic of this condition is severe bilateral atrophy of the caudate nucleus which becomes flattened and concave instead of projecting as a convex rounded eminence into the anterior horn of the lateral ventricle The putamen likewise is shrunken although not to the same degree as the caudate nucleus The globus pallidus is generally affected to some degree but less severely than the caudate nucleus and putamen Microscopically the affected regions show severe nerve cell loss with corresponding reactive glial changes Small nerve cells appear to be more affected than the large The disease process may likewise involve the thalamus subthalamic nucleus (corpus Luysii) and dentate nucleus of the cerebellum Other portions of the nervous system are generally spared and there are as a rule no characteristic visceral lesions

Clinical Aspects This distressing condition generally makes its appearance in early to middle adult years in what ordinarily would be the most effective and productive period of a person s existence Its typically hereditary nature has been emphasized but it is not at all rare for sporadic cases to occur The involuntary movements (bizarre grimacing respiratory irregularity faulty articulation of speech and irregular arrhythmic unpatterned movements of the limbs which impart to the gait a peculiar dancing quality) tend to be less quick and more athetoid than in Sydenham s chorea (see Chap 26) Occasional cases have been reported which on genealogic and pathologic grounds must be classified with Huntington s chorea and yet have shown progressive rigidity rather than choreiform movements As a general rule dementia runs parallel with the motor disorder but occasionally it may appear before chorea or is lacking altogether The advance of the disease is slow with increasing disability from the involuntary movements and the mental changes and is terminated after many years by death from intercurrent infection or not rarely by suicide

Differential Diagnosis There is no difficulty in the recognition of typical cases The relatively late onset progressive course dementia and lack of association with rheumatic fever help to exclude Sydenham s chorea Differentiation from hepatolenticular degeneration (Wilson s disease) which may display similar clinical changes is made by the absence in Huntington s chorea of liver disease or corneal Kayser Fleischer rings and of the characteristic biochemical abnormalities (increased copper excretion aminoaciduria) Sporadic cases of choreiform movements beginning in middle or late life may present a difficult problem in exact diagnosis The occasional cases of violent choreiform movements produced by vascular lesions classically in the subthalamic region are characterized by sudden onset unilateral distribution (hemiballismus) and a tendency to improve after a period of initial severity Virus encephalitis may occasionally be associated with choreiform movements acute development fever and pleocytosis in the cerebrospinal fluid help in recognizing such cases which can further be identified by appropriate virologic studies Although it occurs rarely self limited chorea may appear in older people without identifiable cause

Cerebrocerebellar Degeneration

The progressive cerebellar degenerations of late life and some cases of spinocerebellar degeneration may be accompanied by significant dementia the pathologic basis for which is not always easily demonstrated These disorders are dealt with more fully below in the section devoted to conditions manifested by ataxia

Jakob Creutzfeldt Disease

This designation serves to set apart a group of cases in which relatively rapidly progressive widespread neuronal degeneration occurs in adult life The original descriptions were by H G Creutzfeldt (1920) and A M Jakob (1921 and later) Since then additional studies of similar cases by a number of authors have led to the emergence of a more or less well defined clinicopathologic syndrome within which there is however considerable variability both clinically and pathologically Although most cases occur sporadically hereditary incidence is now clearly established in one family on record

Pathology Although gray matter structures at all levels may be involved the disease often affects most severely the cerebral cortex where it results in devastating neuronal destruction and intense reactive glial changes In places the cortex may be reduced to a network of astroglial fibers almost devoid of nerve cells to which the term *status*

spongiosus has been applied The additional nerve cell loss in the corpus striatum and anterior horns of the spinal cord led to the application of the term *corticostriatospinal degeneration* to this condition by S A K Wilson (1940) Much more circumscribed distribution of what apparently is the same disease process has been described in cases with principally occipitoparietal localization by Heidenhain (1949) and Meyer Leigh and Bagg (1954) Evidence for an inflammatory process is lacking There are no significant vascular lesions and no relevant changes in other organs

Clinical Aspects Most of the cases described have begun in middle age or later but the disorder may occur in young adults As might be expected from the variable distribution of the pathologic effects no uniform clinical picture is encountered but common to all cases is a rapid deterioration of mental powers to which a delirious state may be superadded Additional neurologic manifestations include variable rigidity myoclonic jerks tremors unsteadiness of stance and ataxia of gait and slurring of speech Deep reflexes may be exaggerated normal or absent the plantar reflex is usually bilaterally of extensor type (Babinski sign) In the variety originally described by Heidenhain with severest changes in the occipital lobes significant impairment or loss of vision is an early sign Defective swallowing and stupor or coma usher in the end The total course of the illness is generally less than a year from onset and may be confined to a few weeks or months the longest reported duration is 3¼ years Laboratory investigations including cerebrospinal fluid examination disclose no remarkable findings

Differential Diagnosis When syphilis or other infection has been excluded by appropriate blood and cerebrospinal fluid examinations and serologic tests and the possibility of an overwhelming intoxication has been eliminated no treatable condition remains with which this rare disorder could be confused The florid mental and neurologic changes are unlike any syndrome encountered with vitamin B deficiency A rather similar picture may be met in occasional cases of rapidly growing infiltrating glioma multiple carcinoma metastases virus encephalitis or diffuse abnormality of neuronal or myelin lipid metabolism (see below) The frequent combination of arrhythmic myoclonus and dementia places this disease along with "inclusion body" and sclerosing encephalitis and retinocerebral lipoidosis (Tay Sachs disease) as causes of myoclonic dementia Ultimately the diagnosis depends on pathologic examination

Amaurotic Family Idiocy and Other Lipoidoses

The conditions here to be considered differ from other heredodegenerative disorders in that the underlying biochemical abnormality is better defined They are characterized by a more or less widespread derangement of lipid metabolism which results in abnormal accumulations of lipids in the cytoplasm of cells of the nervous system and often of other organs as well (For information relating to the problem of the lipoidoses in general Chap 98 should be consulted) This process leads to abnormal function and eventually death of the affected nerve cells There is ample evidence for hereditary transmission of these disorders the basis for which is presumed to be a genetically determined abnormality of enzymes concerned with intracellular lipid metabolism What specific enzymes are affected and the exact details of the biochemical derangement have yet to be learned although considerable progress has been made in identifying the lipids involved As far as is known these substances are not foreign to the body or even to the cells in which they accumulate but instead are normally present there but in much smaller quantities No single entirely satisfactory term under which to classify these neurologic disorders has become generally accepted That most frequently encountered in the literature is *amaurotic family idiocy* which cannot however be accurately applied to cases of the disorder without blindness (amaurosis) or mental defect severe enough to be called idiocy Cerebromacular or retinocerebral" degeneration focuses too much attention on the macula or retina to be entirely satisfactory Probably a general name such as lipoidoses of the nervous system" would be the least objectionable lacking though it is in picturesqueness and appeal to the imagination

Special Clinical Types The general type known as amaurotic family idiocy can be further subdivided into varieties which differ from one another in age of onset and extent and location of the pathologic process Thus there are recognized

Tay Sachs Disease This classic form occurs in infants and has extremely widespread involvement including prominent retinal changes (macular cherry red spot) and a rapid progression of impaired motor control of trunk and limbs hypotonia with retained reflexes or mild spasticity seizures and impaired vision usually resulting in death by the third year of life

Late Infantile Form (Bielschowsky) This disease has a more chronic course and results in optic atrophy rather than macular cherry red spot spastic or hypotonic weakness of the limbs cerebellar ataxia tremor and other abnormalities of posture and movement seizures and mental deterioration Death usually occurs by the tenth or twelfth year

Juvenile Form (Spielmeyer II Vogt) Here the onset is still later and the course is prolonged (6 to 7 years or more) with a tendency to pigmentary

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The progressive cerebellar degenerations of late life and some cases of spinocerebellar degeneration may be accompanied by significant dementia the pathologic basis for which is not always easily demonstrated These disorders are dealt with more fully below in the section devoted to conditions manifested by ataxia

Jakob Creutzfeldt Disease

This designation serves to set apart a group of cases in which relatively rapidly progressive widespread neuronal degeneration occurs in adult life The original descriptions were by H G Creutzfeldt (1920) and A M Jakob (1921 and later) Since then additional studies of similar cases by a number of authors have led to the emergence of a more or less well defined clinicopathologic syndrome within which there is however considerable variability both clinically and pathologically Although most cases occur sporadically hereditary incidence is now clearly established in one family on record

Pathology Although gray matter structures at all levels may be involved the disease often affects most severely the cerebral cortex where it results in devastating neuronal destruction and intense reactive glial changes In places the cortex may be reduced to a network of astroglial fibers almost devoid of nerve cells to which the term *status*

superficial resemblance to Schilder's disease (encephalitis periaxialis diffusa) which is best considered as a particular form of multiple sclerosis *in fact* the leukodystrophies have frequently been grouped together as *familial Schilder's disease* The best evidence at present indicates however that the leukodystrophies represent disorders of the metabolism of the myelin sheath lipids and thus as has been frequently pointed out are most closely related to the neuronal lipoidoses previously considered The leukodystrophies can be further classified on the basis of histopathologic and histochemical differences into a number of subtypes which are considered below

Pathology The distinguishing feature is diffuse symmetric breakdown of the white matter of the cerebral hemispheres in which as a rule axones suffer damage to approximately the same degree as the myelin sheaths Also characteristic is the presence within the devastated regions of lipid breakdown products of the myelin sheaths which show distinct histochemical differences from the lipid products encountered in virtually all other destructive processes of myelin (such as infarction traumatic necrosis secondary fiber tract degeneration the demyelinative lesions of multiple sclerosis or Schilder's disease etc) In startling contrast to the extensive white matter lesions is the relative intactness of the nerve cell bodies

Metachromatic Leukoencephalopathy In a large group of cases the lipid breakdown products display the staining reaction called *metachromasia* to a degree and intensity encountered in no other nervous system disease In several cases myelin at every level in the central and peripheral nervous system has shown this abnormality and engorgement of nerve cell bodies with similar metachromatic lipid has regularly been found in anterior horn cells of the spinal cord dentate nuclei of the cerebellum and in some of the nuclei of the brain stem and basal ganglions but oddly enough not in the cerebral cortex The appearance of such cells is strikingly reminiscent of that in conditions such as amaurotic family idiocy (see above) but the location and the histochemical behavior of the involved cells are different The chemical nature of this metachromatic lipid which has also been found by several observers in Kupffer cells of the liver and in kidney tubule cells is still under investigation Studies so far carried out indicate that it consists of lipid material normally present in myelin but that presumably because of a disorder of the metabolic turnover in myelin lipids it accumulates in abnormal amounts

The form of leukodystrophy with metachromatic breakdown products has been encountered in infants children and young adults and in familial and sporadic cases It has not so far been found in old age The familial diffuse cerebral sclerosis of Scholz has been shown clearly to belong to this group and the similar familial cases of Bielschowsky and Henneberg almost surely do One is therefore justified in classifying this form of the disorder as leukodystrophy of the *Scholz Bielschowsky Henneberg type* or *metachromatic leukodystrophy*

Krabbe Form of Leukodystrophy In this form first described as a familial disorder of infants the lipid breakdown products are also atypical of most pathologic processes which destroy myelin but they differ from those described above in a number of histochemical particulars including absence of metachromasia Typical of this disorder is the occurrence of unusual multinucleated cells with phagocytic properties like foreign body giant cells within which the lipid breakdown products are contained Recent studies have indicated that cerebrosides predominate in the phagocytized lipid This suggests a link with Gaucher's disease although the visceral lesions of the latter condition are absent

More recently cases have been described of a very chronic form occurring in the presenile period in which the atypical lipid products most closely resemble the lipofuscins the "wear and tear" lipid pigment of advancing age

Pelizaeus Merzbacher Form In this form characterized clinically by pronounced familial tendency and very chronic course the myelin lesions tend to be patchy and irregular in contrast with the other forms and there is relative sparing of axones Another distinguishing feature of this condition is that the breakdown products of the myelin although very sparse (as would be expected from the prolonged evolution of the disorder) are of the usual fatty variety rather than the more complex lipids found in the conditions described above

Clinical Aspects The symptoms and signs are those of a progressive dementia often associated in the early stages with weakness and unsteadiness of gait and relatively early signs of corticospinal tract disorder Generalized convulsive seizures may occur but are not invariable No clinical phenomena clearly serve to differentiate leukodystrophy from other diffuse progressive cerebral diseases In the form with metachromatic breakdown products of myelin it is possible to demonstrate metachromatic lipids in the urine which do not occur normally or in other diseases (Austin 1957) In this way the diagnosis can be made during life

Differential Diagnosis Familial occurrence signs referable to a disorder of long projection and association fiber systems and relative lack of convulsive manifestations may suggest the diagnosis during life Otherwise the identification of these conditions requires pathologic examination except in so far as it may be possible to identify the metachromatic

degeneration of the retina (a form of retinitis pigmentosa) Blindness imbecility cerebellar ataxia myoclonic epilepsy and pyramidal tract signs comprise the picture

Adult Form (Kufs, Hallervorden) This is considerably rarer than the childhood varieties The nervous system changes tend to be much less widespread than at earlier ages with corresponding differences in the clinical manifestations and blindness is not nearly so constant a feature Dementia seizures and athetosis have characterized some of the cases The course is much prolonged some patients having lived for 10 or more years after the onset of the illness

In all these diseases, lipids of the class of the gangliosides (Klenk) accumulate in the largest amounts other lipids are less conspicuous Lipoidosis of other organs is slight or absent in this group Of interest is the fact that virtually identical ganglioside accumulation has been demonstrated in the nervous system in gargoylism (lipochondrodystrophy) a rare infantile disorder with bony deformities in which there is abnormality in the formation of connective tissue structures as well (Chap 253)

Niemann Pick Disease This condition in which there is striking enlargement of the liver and spleen because of large amounts of phagocytal lipid in those organs is likewise characterized by extensive lipoidosis of the nervous system which histopathologically appears exactly the same as that in amaurotic family idiocy However in this instance sphingomyelins are greatly increased and the gangliosides only slightly so Similar nervous system lesions have been demonstrated in a few cases of infantile *Gaucher s disease* but not in adult forms The lipid involved appears to be of the class of cerebrosides and the gangliosides were not elevated

PATHOLOGY The characteristic pathologic change is engorgement and distention of nerve cell bodies with the lipids concerned In infantile or childhood cases this is so extensive that all nerve cells in every location including those in peripheral ganglions show this alteration As a rule there is evident breakdown and disappearance of nerve cells and in relation to these destructive phenomena prominent reactive glial changes In infantile cases the lipoidosis of the ganglion cells of the retina imparts to the retina a pale appearance against which the macula stands out sharply as the classic cherry red spot In juvenile cases with atrophy and pigmentary deposits the deeper layers of the retina as well as nerve cells degenerate and the pigment epithelium proliferates

In severe cases the white matter is usually abnormal also This can often be accounted for by the destruction of nerve cell bodies with consequent degeneration of their axonal processes Occasionally however large *regions of white matter are totally* necrotic to a degree that cannot be accounted for by any secondary change This finding suggests a primary disorder of the structure of white matter as well and is reminiscent of the leukodystrophies to be discussed on the following pages

In older individuals the process is less extensive and it can be stated in general that the older the individual or the more chronic the course the less widespread are the neuronal changes No constant localization of the disorder can be pointed out unless it be in the cerebellum which is nearly always affected in the juvenile forms of the disease In some cases the alterations in the basal ganglions have been particularly prominent

No morphologic features serve to distinguish the neuronal alterations in amaurotic family idiocy from those in gargoylism or Niemann Pick disease The latter variety can however be differentiated histochemically

CLINICAL FEATURES In infants and children the combination of rapidly progressive dementia blindness retinal changes and generalized convulsive seizures *often* with widespread *myoclonic* jerks forms a consistent picture As already noted the characteristic appearance of the macula in infantile cases yields place in older children and young adults to optic atrophy possibly with pigment accumulations in the retina Familial occurrence is prominent In the very rare adult cases there is no single characteristic feature Dementia myoclonic jerks and variable degrees of rigidity spasticity weakness ataxia and involuntary movements may be encountered with a slowly progressive course measured in years At the moment no generally useful biochemical *determinations can* be made during life which will assure the diagnosis of a nervous system lipoidosis

DIFFERENTIAL DIAGNOSIS In typical infantile or childhood cases there usually is no difficulty in recognizing this condition In older children and adults the diagnosis may only be suspected after other diffuse disorders—neoplastic infectious nutritional or toxic—have been eliminated by the various currently used diagnostic measures It should always be considered in myoclonic epilepsy with mental deterioration progressive cerebellar ataxia and progressive dementia with seizures and athetosis

Leukodystrophy (Degenerative Diffuse Cerebral Sclerosis)

This rare group of conditions in which familial incidence has frequently been observed is characterized by a diffuse breakdown of white matter in association with a remarkable sparing of the nerve cell bodies in the gray matt

Hepatolenticular Degeneration (Wilson's Disease)

This condition is discussed on pp 725 to 727

CONDITIONS CHIEFLY MANIFESTED BY ABNORMAL POSTURES OR INVOLUNTARY MOVEMENTS

Paralysis Agitans (Parkinson's Disease)

This by no means rare condition was named and classically described by James Parkinson in 1817 His remarkably complete account gives this definition Involuntary tremulous motion with lessened muscular power in parts not in action and even when supported with a propensity to bend the trunk forwards and to pass from a walking to a running pace the senses and intellects being uninjured"

Typically paralysis agitans is a disorder of middle or late life with very gradual progression and a prolonged course Although it has been seen to occur in families (the estimated familial incidence is 6 per cent) it usually is sporadic It bears no consistent relationship to any known disease process such as arteriosclerosis trauma or intoxication although such conditions have often been invoked as etiologically significant and may at times produce somewhat similar clinical manifestations It is well recognized however that the epidemic encephalitis of von Economo which occurred in a world wide distribution in the years following the First World War was followed in a considerable number of cases by a syndrome clinically indistinguishable from paralysis agitans It is usual in such instances to speak of *postencephalitic parkinsonism* whereas the term *Parkinson's disease* should be reserved for true paralysis agitans of unknown cause

Pathology Despite the general familiarity with the condition and an extensive literature on the subject it cannot be said that the pathology of paralysis agitans is yet fully understood The only regularly observed changes have been in the aggregates of melanin containing nerve cells in the brain stem (substantia nigra locus caeruleus dorsal motor nucleus of the vagus) where varying degrees of nerve cell loss with reactive gliosis most pronounced in the substantia nigra along with distinctive eosinophilic intracytoplasmic inclusions (*Lewy bodies* after their description by F H Lewy in 1913) are a consistent finding Changes have also been seen in other structures of the basal ganglions but they are not clearly different in nature or degree from what may be encountered in other patients of similar age without extrapyramidal motor disorders It is tempting therefore to consider paralysis agitans as belonging with the system diseases the affected system being that of the pigmented nuclei of the brain stem It is noteworthy that similar changes in the same groups of melanin-containing cells are likewise found in postencephalitic parkinsonism which pathologically as well as clinically may be extremely difficult to distinguish from paralysis agitans

Clinical Aspects In its fully developed form this disorder cannot be mistaken for any other The stooped posture the stiffness and slowness of movement the rigidity of facial expression and the rhythmic tremor of the limbs which subsides on active willed movement or complete relaxation are familiar to every clinician Although symmetric in the later stages the disorder typically begins asymmetrically e g as a slight tremor of the fingers of one hand or in one leg Also typical is more or less general stiffness of the musculature subserving posture so that even where tremor is inapparent the disease may betray itself by a somewhat staring and immobile facial expression a monotonous voice a general slowness of all motor activity and a curious lack of the little spontaneous movements of postural change that are so characteristic of the normal individual When tremor is minimal patients often are able to alleviate it by resting their hands on a table or the arms of a chair or by keeping them in their pockets The tremor although fluctuating from moment to moment in amplitude and distribution is perfectly regular at a rate of about 4 to 6 per second A fine more rapid tremor may be seen in the early stages of the disease whereas a more violent trembling of greater amplitude characterizes the later course The tremor is generally most pronounced in the hands but may involve also the legs (and thus secondarily the trunk) lips tongue and neck muscles and is easily seen in the eyelids when they are lightly closed There is no total paralysis although general enfeeblement of voluntary movement is characteristic of the fully developed disorder Together with the stooped attitude there is a typical "festinating gait whereby the patient prevented by the abnormality of postural tone from making the appropriate reflex adjustments required for effective walking progresses with quick shuffling steps at an accelerating pace as if to catch up with his center of gravity Clinical examination of the tendon and plantar reflexes discloses no abnormalities There are no sensory changes although deep aching in joints and muscles is common Eventually the patient may become so incapacitated by rigidity and tremor as to be helpless in caring for himself It has often been observed however that even severely disabled patients may under great emotional stress perform complex motor acts quickly and efficiently in a manner that ordinarily would be impossible for them Thus a patient may be able to jump up

variety by appropriate examination of urinary sediment

Progressive Familial Myoclonic Epilepsy

This rare disorder forms a distinct clinicopathologic syndrome characterized by recessive heredity Typically it appears in childhood or early adult life beginning with generalized convulsive seizures which are followed after an interval of years by *myoclonic jerks* of increasing frequency and severity and progressive dementia with death before *middle age* The pathologic features suggest a disorder of nerve cell metabolism the nature of which remains unidentified A link with amaurotic family idiocy is present in a few cases but this does not hold true for all

Pathology In many of the cases on record there are distinctive intracytoplasmic inclusion bodies within nerve cells which may be found at all levels in the central nervous system although they are most frequent in the dentate nucleus of the cerebellum substantia nigra and thalamus These bodies which on the basis of recent histochemical studies react like an acid mucopolysaccharide and which have long been known to have staining properties like amyloid were initially described by Lafora (1911) and are generally known as *Lafora bodies* In addition to these inclusions there is always some degree of nerve cell loss in gray matter structures together with some reactive gliosis In a recently described case with typical clinical findings and pathologically numerous Lafora bodies in brain and spinal cord there was material similar in histochemical reactions to the Lafora bodies contained within heart muscle fibers and liver cells (Harriman and Millar 1956) Some cases have been described with typical clinical features and with degenerative changes in the nervous system similar to those in other cases of this syndrome but with absence of Lafora bodies A few cases are on record in which an indistinguishable clinical picture was associated with the typical pathologic findings of amaurotic family idiocy

Clinical Aspects The onset in most cases is at about the time of puberty or a few years before or after it There is nothing distinctive about the convulsive seizures with which the disorder generally begins The myoclonic jerks are sudden asymmetric or symmetric brief contractions of muscle groups of the limbs face and trunk occurring arrhythmically and unpredictably usually with sufficient force to displace the parts affected They characteristically are provoked by all sorts of stimuli as well as occurring spontaneously and may be so severe as to interfere seriously with willed movements or may cause the patient to fall abruptly The disorder progresses gradually running a course measured in years with terminal stages characterized by profound dementia and total helplessness Treatment with anticonvulsant medication may relieve the generalized convulsive seizures but has no effect on the myoclonic phenomena or the dementia

Hallervorden Spatz Disease

This unusual disorder often familial is associated with a rather variable clinical picture in which the main features are onset in childhood after normal birth and uneventful development abnormalities of posture and muscle tone with involuntary movements and progressive dementia with death in early adult years or before Pathologically characteristic abnormalities in the basal ganglions suggest a metabolic disorder in these regions The classic features of the condition were described in an affected family by Hallervorden and Spatz (1922)

Pathology The distinctive feature of this condition is the accumulation in the globus pallidus and zona reticulata of the substantia nigra of large amounts of pigmented material which imparts a grossly visible brownish discoloration to these regions Microscopically one sees irregular pigmented concretions and granules of varying brownish or greenish hues depending upon the stains used A considerable number of these show the presence of iron and the local tissue iron is increased in amount It is generally believed that these deposits of material consist of substances normally present in the nuclear regions affected but greatly increased in quantity There is no systemic disorder of iron metabolism Destruction of nerve cells is present in these regions and likewise to some extent in the cerebral cortex although it generally is not so severe as in other forms of heredodegenerative brain disease and is overshadowed in severity by the pigmentary disorder in the basal ganglions

Clinical Aspects The disorder typically makes its appearance in childhood or adolescence with abnormalities in muscle tone and movement such as rigidity and choreoathetosis Abnormal postures of the trunk characteristic of torsion spasm (dystonia) may be seen Speech becomes indistinct and there is progressive intellectual impairment Eventually the involuntary movements give way to increasing generalized rigidity and death comes as a rule about 10 years after onset

Differential Diagnosis No feature of the clinical picture serves to distinguish this particular disorder from other conditions showing dementia with extrapyramidal motor abnormalities Hepatolenticular degeneration must be excluded by appropriate laboratory tests The clearly progressive course sets this condition apart from clinically similar abnormalities resulting from accidents or illnesses at birth or in the neonatal period

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tense and restless may require judicious use of sedatives

In recent years surgical methods for relief of parkinsonism have received increasing attention and in a few cases the results have been so dramatic and gratifying that this approach to treatment of the disorder cannot be overlooked At present the most effective procedure is the destruction by necrotizing chemical agents or ultra-high frequency electromagnetic vibrations of structures in or near the globus pallidus It seems paradoxical that the effects of a spontaneously destructive lesion of nerve cells in one part of the brain could be overcome in any way by artificially producing additional destructive lesions in another part and yet the practical results show that this is possible No certain knowledge so far exists as to the exact anatomic or physiologic effects of these surgical lesions despite their pragmatic usefulness in selected cases The surgical methods are still in the experimental stage are not without danger and cannot be fully endorsed at this time

Dystonia Musculorum Deformans (Torsion Spasm)

This is a clinical term denoting a state characterized by slow nonrhythmic involuntary movements which produce abnormal at times bizarre postures of the trunk and limbs With passage of time these postures tend to become more or less fixed Underlying the clinical disorder may be any of a number of pathologic conditions such as the residual lesions of epidemic encephalitis the pigmented deposits of Hallervorden Spatz disease (described above) hepatolenticular degeneration (Wilson s disease) or the scars of cerebral birth injury in the broad sense or kernicterus There remain a few rare cases with relatively early onset and progressive course occurring as an hereditary disorder in some instances which justify their consideration as a separate entity

Pathology Very few cases have been studied pathologically In some the caudate nucleus and putamen were the chief sites of disease in others the globus pallidus was affected without significant alteration of other parts of the corpus striatum In addition lesions have been found in the thalamus and subthalamic nucleus in a few instances The abnormalities have consisted of simple cell loss with reactive gliosis without specific features Where torsion spasm has been the major clinical manifestation of one of the diseases mentioned above the distinctive lesions of that particular disorder have been found Whatever their location and nature the pathologic findings are not such that the clinical state could be assumed from their presence alone

Clinical Aspects The motor abnormalities are described in Chap 26 In the early stages the involuntary muscular contractions are intermittent and variable in location and severity but typically interfere with motor performance by superimposing an unwanted posture upon parts in use The term dystonia or torsion spasm is used to refer to these phenomena in the muscles of the trunk and proximal joints of the limbs whereas similar slowly changing abnormal postures of the distal parts of the limbs are generally termed athetosis In cases afflicted with the disorder under discussion both types of abnormality may be present Affection of face and tongue muscles results in faulty articulation of speech which eventually becomes incomprehensible The tendon and plantar reflexes which can be assessed only during moments of relaxation of the affected parts are characteristically normal

Dementia is not a necessary accompaniment of the condition except perhaps in the terminal stages but with severe derangement of all available methods of communication an adequate evaluation of mental capacity may be impossible Typical of most cases has been onset in childhood and slow progression with survival into adult life but not into middle age

Differential Diagnosis Hepatolenticular degeneration should be seriously considered in any case presenting these motor symptoms and appropriate measures should be undertaken for its investigation (see Chap 93) The progressive course and possibly the family history differentiate the degenerative group from the "symptomatic dystonias resulting from infections or metabolic disorders occurring at birth or later

Treatment This is most unsatisfactory Dystonia is notoriously unresponsive to drug therapy although antispasmodic drugs such as those used for parkinsonism should be tried Surgical relief has been attempted in a few cases with some promising early results the ultimate value of this form of treatment has yet to be established

CONDITIONS CHIEFLY MANIFESTED BY ATAXIA

The conditions about to be considered are distinguished clinically by progressive unsteadiness in standing and walking with more or less disturbance of the coordination of other motor acts Pathologically they are characterized by degeneration of the cerebellum and/or its related fiber systems and thus constitute classic examples of the system diseases" Although sporadic instances occur hereditary transmission is an outstanding feature in many cases thus this group of disorders is often referred to as the hereditary ataxias Their subdivision into more or less separate entities is largely arbitrary with pathologic changes of varying distribution underlying clinically indistinguishable symptom complexes Furthermore there is considerable over

and run out of a burning building on hearing the call of Fire! —only to be helpless as before once the crisis is past Although the temporary alleviation under extreme provocation can never be long maintained it is nevertheless true that the general severity of the disorder is considerably influenced by emotional factors being aggravated by anxiety tension and unhappiness and minimal when the patient is in a contented frame of mind Despite the inherently progressive nature of the condition much can be achieved with good medical management and patients may continue for years to live effective happy lives in spite of this affliction Intellectual deterioration is not a consistent feature of paralysis agitans but it must be conceded that in very advanced stages of the condition dementia may be encountered

Differential Diagnosis In typical cases this is not difficult The extrapyramidal syndromes associated with most diseases of known cause or established nature such as cerebral vascular disease cerebral hypoxia (including carbon monoxide asphyxia) or metallic poisoning differ from paralysis agitans in a number of respects such as atypical behavior of tremor presence of signs of pyramidal tract deficit or early onset of dementia etc The differentiation from postencephalitic parkinsonism may be impossible a clear history of an attack of epidemic encephalitis (prolonged somnolence disturbance of consciousness diplopia) and relatively early age of onset of the disorder and the presence of tics localized spasms and oculogyric crises may be the only clues to this diagnosis In recent years a neurologic disorder strikingly similar to Parkinson's disease has been seen following the prolonged administration of large amounts of reserpine and similar drugs which subsides on withdrawal of the offending drug—a matter of considerable theoretic and practical importance Parkinsonism is probably never produced by cerebral neoplasm

Treatment Although as with the other degenerative nervous diseases no known treatment influences the underlying disease process patients with paralysis agitans can often be greatly helped by well managed symptomatic therapy As already suggested an important part of any such program is to help the patient by means of sympathetic understanding to comprehend the nature of his illness to accept his fate and to carry on courageously in spite of it The constant tremor and rigidity result in physical fatigue thus patients generally require more rest than previously Physical measures such as cool clothing massage and stretching exercises may promote greater muscular relaxation and alleviate the muscle and joint aching which may be prominent and early symptoms of the disease

Along with these general supportive measures optimum treatment in most cases requires the wise use of antispasmodic drugs singly or in combination The program of medication in each case must be on an individual basis with choice of drugs and adjustment of dosages under close medical supervision until a maximum of therapeutic benefit with a minimum of toxic side effects is achieved At best only a partial relief of symptoms can be expected, with rigidity in general responding better than tremor although even the latter may be considerably allayed in some cases but even partial relief may make the difference between effective living and incapacity

The drug treatment of paralysis agitans (and postencephalitic parkinsonism) is on a purely empirical basis It has long been known that some relief can be obtained with drugs of the belladonna group (atropine scopolamine stramonium) and these substances are still extensively used A number of synthetic antispasmodics have become available and appear to be more effective in many instances than the older forms of medication Preparations of this kind are trihexyphenidyl (Artane) ethopropazine hydrochloride (Parsidol Lysivane) procyclidine hydrochloride (Kemadrin) cycrimine hydrochloride (Pagitane) benzatropine methane sulfonate (Cogentin) and caramiphen hydrochloride (Panparnit) Some of the antihistamines such as phenindamine (Thephorin) and diphenhydramine (Benadryl) have likewise been shown to be helpful A combination of drugs is often better than one alone A recommended program is to begin with Parsidol 10 to 20 mg three to four times daily and to increase this gradually at 3 day intervals to a maximum of one 100 mg tablet four times daily If the patient already is taking one form of medication for this condition and it is desired to substitute another form the older medication must be discontinued gradually by small decrements rather than abruptly while the newer one is being increased to full dosage otherwise a severe increase of rigidity or tremor may occur Toxic effects include nausea lightheadedness drowsiness and particularly in older patients mental confusion often at night These effects subside rapidly when smaller dosage is resumed Once the optimum dosage with this preparation is reached further therapeutic benefit may be achieved by adding other drugs such as Artane (2 mg or 5 mg tablets three to four times daily) or Thephorin (25 to 50 mg three to four times daily) or both It is to be emphasized that any of these drugs should be given to the threshold of toxicity before being discontinued as ineffective and that dryness of the mouth is an unavoidable side effect Occasional patients with drowsiness or sluggishness are helped by the additional use of analeptics (dextroamphetamine 5 mg two to three times daily) but not late in the day so that sleep is not disturbed Patients who are

a distinct entity Marie tried to point out, on the basis of a number of case reports in the literature of the time *that there were other cases of hereditary ataxia* of later onset which could not be fitted into Friedreich s description *He offered the suggestion* that the cerebellum itself was the major site of disease in these cases *Subsequent pathologic examination* of the cases he reviewed have shown that he was partly in error in this supposition nevertheless following his report the concept of Marie s ataxia has become firmly established in the writings on hereditary ataxia Thus on the basis of tradition and clinical convenience it is retained here

Pathology As indicated above and as with the late life ataxias there is no one characteristic pathologic change in this group of cases even *though the clinical disorder is identical* Some patients have had degenerative changes in the spinal cord indistinguishable from those of Friedreich s ataxia Others have shown cerebello-olivary degeneration or olivopontocerebellar atrophy

Clinical Aspects The principal basis for separating out this group of cases is their onset in early adult life and their hereditary nature The signs of an associated chronic peripheral neuropathy so distinct a feature of Friedreich s ataxia are not prominent in this group In general the clinical features are those already described above Signs of pyramidal tract deficit are variably present and dementia occurs in some cases A relatively long course can be expected (about a decade or possibly two) although death from intercurrent disease comes earlier than would be expected for the ordinary healthy individual

Friedreich s Ataxia

This classic form of hereditary ataxia, first clearly depicted by Nikolaus Friedreich of Heidelberg in 1863 forms a relatively distinct symptom complex which generally runs true to form although it overlaps other heredodegenerative syndromes particularly chronic peripheral neuropathies and progressive optic atrophy conditions to be discussed subsequently Friedreich s ataxia is typically a disease of childhood or adolescence although onset at a somewhat later age has occasionally been seen In some families the disorder occurs with dominant inheritance it is a recessive trait in others

Pathology The outstanding abnormalities are in the spinal cord and peripheral nerves and are typical of a chronic degenerative process In the cord the principal changes are in the sensory fibers of the posterior columns in the spinocerebellar tracts and in the lateral corticospinal (pyramidal) tracts Additional lesions of varying extent may be found in the brain stem and in the cerebellum itself although the latter structure is often intact Involvement of other parts of the central nervous system at even higher levels occasionally occurs In the *peripheral nerves the lesions vary likewise in severity* and extent They resemble those encountered *in the chronic peripheral neuropathies described* below Thus even so relatively discrete an entity *as the Friedreich form of hereditary ataxia is neuro*pathologically far from homogeneous In some cases there is a peculiar form of myocardial degeneration resulting in thickening and fibrosis of the myocardium No other visceral lesions are regularly encountered

Clinical Aspects As with other progressive ataxias the disorder first appears in the legs Thus the child patient previously healthy begins to stagger and lurch in walking and is unsteady often in a tremulous fashion on standing Clumsiness and *intention tremor of the hands and arms appear later* along with faulty articulation and abnormal rhythm (scanning) of speech The limbs in addition to being ataxic generally show considerable weakness Examination usually discloses nystagmus and skeletal deformities—kyphoscoliosis the basis for which is not certain and a peculiar foreshortening and high arching of the feet (pes cavus) with cocking up of the toes sometimes called the *Friedreich foot* Typically there is the unusual combination of total absence of deep (tendon) reflexes with extensor plantar reflexes (Babinski sign) Position and vibration senses in the legs are usually impaired and often in the hands as well In some patients impairment of cutaneous sensation (pain and temperature light touch) is demonstrable in a roughly stocking and glove distribution The optic disks may be pale indicating optic atrophy although actual blindness is relatively rare Some patients are of low intelligence or may become demented in the course of the disease Survival beyond early adult life is rare with death frequently the result of associated myocardial disease

Occasionally very mild or fragmentary forms of the disorder (such as pes cavus and absent or hyperactive tendon reflexes) may be encountered with little if any disability or progression Such abnormalities are most likely to be seen in other members of the family of a patient afflicted with the fully developed form

Differential Diagnosis The classic form of Friedreich s ataxia is readily recognizable and cannot easily be confused with other conditions It is to be expected however that variations in the clinical manifestations may occur because of the variable pathologic changes One particularly well known variant was described in 1926 by Levy and Roussy in which the muscle wasting of the legs is severe and is combined with areflexia and a sensory ataxia There have been reports of Friedreich s ataxia in some members of a family and of the Levy Roussy

lapping with other forms of hereditary nervous disease so that in a given case a remarkable combination of defects may be encountered These facts have led to the idea that in this group there is a set of closely related genetically determined abnormalities which may occur together in an almost infinite series of combinations so that it is not possible to separate out well defined disease pictures Nevertheless certain constellations of symptoms and pathologic findings occur with sufficient regularity to warrant their separation for purposes of discussion The classification about to be given is not entirely satisfactory but is designed to be of practical help to the physician confronted with a case

Cerebellar Degenerations of Late Life

These disorders present themselves clinically as progressive ataxia beginning in middle age or later Most sporadic cases come into this group but there are some cases of hereditary ataxia as well which do not make their appearance until the later years of life The rare form of spinocerebellar degeneration associated with the presence of carcinoma *subacute carcinogenic spinocerebellar degeneration* can also be considered here although its relationship to the spontaneously occurring forms is not at all clear

Pathology There is grossly visible atrophy of the cerebellum which may be most striking in the superior aspect of that organ or in the midline (vermis) but may affect the entire cerebellum Microscopically there is widespread loss of nerve cells in the cerebellar cortex chiefly affecting the Purkinje cells but often involving the granule cells as well When the abnormalities are so confined it is usual to speak of *cortical cerebellar atrophy* Closely related and perhaps basically identical is *cerebello olivary degeneration* where in addition to atrophy of the cerebellar cortex there is nerve cell loss in related parts of the inferior olivary nuclei of the medulla oblongata generally interpreted as transsynaptic degeneration secondary to the disease process in the cerebellar cortex In another striking group of cases there is in addition severe degeneration of the pontine nuclei and middle cerebellar peduncles this is called *olivopontocerebellar degeneration* In such cases there may be degenerative changes in other neuronal systems particularly the cerebral cortex and basal ganglions More rarely in the late life group disease may be found in the spinal cord affecting posterior columns spinocerebellar tracts and corticospinal tracts in varying combinations such lesions are more characteristic of the hereditary group or the form associated with carcinoma than of sporadic cases

Clinical Aspects The disorder almost always makes its appearance first in the legs resulting in unsteadiness of stance and gait of the peculiar wavering lurching character so typical of cerebellar ataxia (see Chap 26) Disturbance in articulation and rhythm of speech occurs early in the disease and may progress to total incomprehensibility After the lapse of years the arms likewise become ataxic although in older individuals death may supervene before this stage is reached Nystagmus may occur but it is often absent In some cases there is exaggeration of deep reflexes with extensor plantar responses and in a few (e g with olivopontocerebellar atrophy) there may be rigidity and Parkinson like tremor in addition to the ataxia A number of patients have shown progressive dementia so that it is proper to speak of such patients as having a cerebrocerebellar degeneration Progression is very gradual and slow being measured in decades and may not necessarily shorten life In the cases associated with carcinoma the tempo of evolution of the process is much more rapid with severe disability coming on within a period of months There is no response to any known form of treatment in any of the progressive ataxias although encouragement and gait training may enable a patient to overcome his disability to some extent

Differential Diagnosis The slow but relentless progression in the absence of increased pressure or signs of inflammation in the cerebrospinal fluid serve to distinguish this degenerative group from other forms of cerebellar ataxia such as may occur with neoplastic infectious or demyelinative disease drug intoxications (e g barbiturates) or heat stroke (onset of cerebellar ataxia during periods when temperature is 106 F or over) The degenerative disorders under discussion tend to occur in a setting of otherwise good general health this together with other clinical differences distinguish them from the ataxia of deficiency disease such as the Wernicke Korsakoff syndrome (see Chap 258) The carcinogenic form of spinocerebellar degeneration may be distinguished from direct carcinomatous involvement of the nervous system by the symmetry of the findings and the absence of increased intracranial pressure The alcoholic cerebellar degeneration usually develops rapidly and then remains more or less stationary for the remainder of the patient s life (cf Chap 258)

Hereditary Ataxia of Pierre Marie

Included here are cases of hereditary progressive ataxia with onset in early adulthood which conform neither to the typical syndrome of Friedreich s ataxia (to be described below) nor to the late life ataxias just discussed Considerable doubt has been raised as to the validity of retaining the concept of Marie s hereditary ataxia because pathologically this is by no means a uniform group When Pierre Marie wrote about the subject in 1893 Friedreich s ataxia had relatively recently become recognized as

erally suffices in such instances to exclude serious neurologic disease

Progressive weakness from intrinsic disease of muscle (myopathy polymyositis) may occasionally be difficult to distinguish from progressive muscular atrophy of the type under discussion yet the differentiation is important from the standpoint of prognosis or treatment Under such circumstances the diagnosis can be made by muscle biopsy and electromyography

Infantile Muscular Atrophy (Werdnig Hoffmann) Amyotonia Congenita (Oppenheim)

The form of progressive muscular atrophy described by Werdnig and Hoffmann is a disease of infants and young children typically afflicting several members of a family Pathologically it closely resembles the adult disease described above *Amyotonia congenita* is a purely clinical term used to designate abnormal laxness of somatic musculature observed at birth or in early infancy it may occur in a number of different pathologic processes including the Werdnig Hoffmann disease For further details of these conditions Chap 253 should be consulted

Hereditary Spastic Paraplegia

This very rare disorder is characterized by early onset (childhood or adolescence) and slow progression of weakness and spasticity of the legs Later the arms may be affected usually to a lesser degree The pathologic changes closely resemble those of Friedreich s ataxia and there is reason now to believe that this condition is in fact an incomplete form of Friedreich s disease in which spastic weakness overshadows minimal or absent ataxia and sensory changes The diagnosis is made by the family history and by excluding other possible causes of bilateral spastic weakness of the limbs The relationship to Friedreich s ataxia is further confirmed by the occurrence in some cases of pes cavus and optic atrophy One group of these patients also suffers a progressive dementia

CONDITIONS COMBINING MUSCULAR WEAKNESS AND WASTING WITH SENSORY CHANGES

Syringomyelia and Syringobulbia

Among neurologic diseases this condition characterized by cavity formation in the spinal cord or medulla is not at all rare There is no universal agreement as to its nature although in general it is considered to belong in the class of developmental disorders or embryologic malformations Yet the usual onset of disability in adult life (before middle age) and its progressive course as well as its unknown cause are features it shares in common with many of the degenerative diseases Familial syringomyelia has been reported but is extremely rare the cases generally seen are sporadic

Pathology The cavity (Greek *syrinx* "pipe" or "tube) is most frequently located in the cervical enlargement of the spinal cord Typically it is independent of the central canal of the cord but lies dorsal to it and extends laterally and posteriorly into one or both posterior horns of gray matter and sometimes anteriorly into the ventral horn it also has a long vertical extent through many segments of the cord Usually the cavity is lined with sparsely cellular astrocytic glial tissue but when it communicates with the central canal (as it does in some cases) it may be lined in places with ependymal cells The cavity is virtually always in a position to interrupt the crossing fibers carrying pain and temperature sensations and if it is sufficiently large it involves as well the anterior horns and lateral corticospinal tracts In far advanced cases the cord is reduced to a thin hollow shell distended with cerebrospinal fluid under such circumstances the cord may rarely occupy the entire space in the vertebral canal producing spinal subarachnoid block Syrinx formation occurs much less frequently in the lumbosacral cord where it has the same characteristics as in the cervical region In occasional cases cavitation may extend all the way up and down the cord The cavity has a very typical location in the medulla seen in cross section it forms an oblique slit extending from the floor of the fourth ventricle between the hypoglossal nucleus and dorsal motor nucleus of the vagus to the periphery immediately dorsal to the inferior olive This results in significant clinical effects discussed below Although typical syringomyelia may be found in association with tumors within the spinal cord such as intramedullary glioma or hemangioblastoma the condition does not necessarily depend on the presence of neoplasms Frequently there are other defects or malformations in other organs such as abnormalities of the skull or cervical spine or spina bifida but these are not constant, although kyphoscoliosis to which reference is made below is regularly found

Clinical Aspects The symptoms and signs are referable to an asymmetric but centrally placed lesion in the spinal cord (cf Chap 27) Because of the effect on sensory pathways sensory abnormalities are nearly always found At first there is loss of pain and temperature sensation alone—a defect of which the patient may not be aware—which extends most typically over the shoulders arms and hands in a capelike distribution As the cavity enlarges other forms of sensation may be lost but still in a segmental distribution with intact sensa

syndrome in others In the absence of family history and with atypical clinical findings further diagnostic studies to exclude tumor infections intoxication or congenital malformation will be necessary

CONDITIONS WITH OUTSTANDING MUSCULAR WEAKNESS AND WASTING, WITHOUT SENSORY CHANGES

Motor System Disease

This general term is used to indicate a progressive disorder of motor neurones in cerebral cortex brain stem and spinal cord manifested clinically by muscular weakness with muscle atrophy and spasticity with exaggeration of deep reflexes in varying combination It is a disease of middle life generally appearing in the fifth or sixth decades Customarily a subdivision is made on the basis of the particular grouping of symptoms and signs observed Thus the most frequent form in which muscular atrophy and hyperreflexia are combined is called *amyotrophic lateral sclerosis* Rather more rare are the cases in which weakness and atrophy alone exist without clinical evidence of corticospinal tract dysfunction for these the term *progressive muscular atrophy* is used Where the disorder affects predominantly the musculature innervated by the cranial nerves it is usual to speak of *progressive bulbar palsy* Very rarely the picture is dominated by spasticity and hyperreflexia without obvious muscular wasting such cases are classed as *primary lateral sclerosis* There is no reason to believe that these subgroupings are anything other than clinical variants of the same disease process which is another classic example of a "system disease Most cases are seen as sporadic instances and an hereditary basis was long denied by competent observers Yet there is recent evidence that the disease can occur in its classic form as an inherited disorder not infrequently as a mendelian dominant (Kurland et al 1955)

Pathology There is widespread selective atrophy and loss of motor nerve cells at all levels of the central nervous system Some evidence of disease in the corticospinal motor system is usually found pathologically even when physical signs referable to such changes were not observed during life The spinal cord typically shows some loss of nerve fibers in the lateral and anterior columns in addition to the obvious corticospinal tract degeneration although no clinical changes can generally be related to such lesions The atrophy of fibers in skeletal muscles is typically that due to loss of motor innervation

Clinical Aspects The disease begins insidiously and may be well advanced before the patient is aware of it Although often asymmetric initially the weakness and muscular wasting gradually become symmetric and widespread Classically the disorder becomes first evident in the small muscles of the hands but it may begin in one or both legs or in muscles supplied by cranial nerves Vague feelings of discomfort in the muscles tightness numbness (without objective sensory changes) and recurrent cramps may be early symptoms The progressive atrophy of the musculature is accompanied by widespread visible fascicular twitchings of groups of muscle fibers a classic feature Despite extensive involvement of skeletal muscles generally sphincter control remains intact Sooner or later the disease affects muscles supplied by the brain stem resulting in weakness atrophy and fasciculations in the tongue and facial musculature dysarthria and impairment of chewing or swallowing The functions of the ocular muscles oddly enough are invariably spared Affection of corticobulbar fibers results in such manifestations of pseudobulbar palsy as involuntary weeping or laughter exaggerated reflex movements of the facial muscles of expression and sucking reflexes Progression is unhalting and relatively rapid leading to extensive paralysis with death from respiratory weakness or aspiration pneumonia generally within about 2 years from onset Intelligence and awareness are typically preserved to the end

Differential Diagnosis Other forms of spinal cord disease neoplastic inflammatory or mechanical for which effective treatment is available may at times resemble amyotrophic lateral sclerosis particularly where involvement of the cervical cord (e g spondylosis with osteophytic overgrowth in the cervical spinal canal) produces weakness wasting and fasciculations in the upper limbs and spasticity in the legs The absence of cranial nerve involvement may be helpful in differentiating such cases although some compressive lesions at the foramen magnum may implicate the twelfth cranial (hypoglossal) nerve with resulting affection of the tongue Absence of pain or of sensory changes normal function of bowels and bladder normal roentgenographic studies of the spine and absence of changes in the composition or dynamics of the cerebrospinal fluid are all points in favor of degenerative disease and against other conditions but where doubt exists contrast myelography should be performed Nutritional myelopathy can be excluded by history and on other clinical grounds

Although fasciculations are a prominent feature of motor system disease they are not in the absence of weakness muscle atrophy or loss of tendon reflexes valid signs of it for they may occur in a variety of metabolic or toxic disorders (e g thyrotoxicosis salt depletion) as well as in otherwise healthy individuals Careful clinical evaluation gen

described by Refsum (1946) and called by him *heredopathia atactica polyneuritiformis* in which peripheral neuropathy and ataxia are associated with progressive nerve deafness retinitis pigmentosa and a high cerebrospinal fluid protein Although the pathologic background of this particular variety is yet to be fully investigated some of the findings suggest changes in the central nervous system resembling those of amaurotic family idiocy (neuronal lipoidosis) in addition to lesions much like those in Friedreich's ataxia

Pathology The lesions are typical of a chronic multiple peripheral neuropathy with secondary atrophic changes in muscles The atrophic process in the nerve fibers is associated with some abortive regenerative phenomena and with proliferation of connective tissue and Schwann cells which in the hypertrophic variety may reach extreme degrees In such cases and also in some others where the nerve trunks were not enlarged the spaces between the remaining fibers are filled with a peculiar loose textured connective tissue in the interstices of which there is a mucinous fluid—a characteristic but still unexplained abnormality In the central nervous system there are varying degrees of overlap with the lesions found in the various forms of hereditary ataxia already discussed

Clinical Aspects The disorder usually begins in childhood and progresses very slowly In the classic cases of peroneal muscular atrophy the combination of pes cavus with extreme atrophy of the anterior tibial and calf muscles (stork legs) and wasting of the lower thigh musculature (giving an appearance like an inverted champagne bottle) presents a striking picture There is total absence of deep reflexes and sensation is altered as described above under Friedreich's Ataxia The possibility of combinations with other hereditary neurologic syndromes has already been pointed out Although death in a state of extreme debility in early adult life is common progression in some cases may be extremely slow and may lead to very little disability

Differential Diagnosis It may be necessary to exclude chronic intoxications that produce polyneuropathy (lead arsenic chronic medication with isonicotinic acid hydrazide) or nutritional neuropathy or multiple neuropathy with malignant neoplasms (bronchogenic carcinoma multiple myeloma) or amyloid neuropathy but in general these conditions are sufficiently unlike the heredodegenerative forms to prevent confusion with them Apart from the family history the early onset and slow progression in the face of good general health the absence of significant cerebrospinal fluid changes and generally distinctive pattern of involvement are sufficient for the accurate recognition of the degenerative neuropathies In occasional sporadic or atypical cases biopsy of muscle and of a small cutaneous nerve twig (most conveniently the sural cutaneous nerve) will be necessary

Treatment Although no specific treatment is available patients whose disease is of slow progression and in whom conditions are otherwise favorable may be greatly helped by measures to ensure a stable walking surface such as corrective shoes braces to prevent foot drop and even orthopedic procedures to stabilize the joints

CONDITIONS CHIEFLY MANIFESTED BY VISUAL LOSS

As already stated in previous sections progressive impairment or loss of vision due to degenerative changes in the visual system (retinas and optic nerves) may be an accompaniment of morbid processes affecting the nervous system diffusely—in particular the nervous system lipoidoses and the large group of the hereditary ataxias Occasionally however the peripheral visual system is the major or only site of disease In such cases the disorders are strongly hereditary For detailed discussion of these conditions standard reference works on ophthalmology should be consulted Nevertheless two entities because of their close relationship with other degenerative diseases of the nervous system warrant some discussion here

Hereditary Optic Atrophy (Leber)

This rare condition is characterized by the relatively rapid development of bilateral blindness with optic atrophy coming on in early adult life It was first thoroughly described by Leber in 1871 Typically it occurs as a sex linked recessive trait chiefly affecting men but it likewise may be seen in women

Pathology In the only recorded case with autopsy the changes occurred primarily in the ganglion cells of the retina with secondary degeneration in optic nerve fibers Because of the limited examination in this case it is not known whether there were lesions in other parts of the nervous system

Clinical Aspects The condition often begins asymmetrically with blurring of vision in one eye followed in days or weeks by similar affection of the other eye Vision then deteriorates rapidly over ensuing weeks or months generally with eventual total blindness as a result although arrest before this stage has been seen or even a little improvement after initial steady progression In the early stages examination of the visual fields shows large central scotomas The optic disks may be normal at first or may be swollen (optic neuritis) later the appearance is typically that of optic atrophy with pale clearly outlined disks

tion in the lower parts of the body As a rule one finds weakness wasting loss of tendon reflexes and fasciculations in the muscles of the hands and arms and spastic weakness with signs of pyramidal tract deficit in the legs If the syrinx extends into the preganglionic center for sympathetic innervation of the pupil in the lateral horn of gray matter at the eighth cervical to first thoracic levels this results in Horner's syndrome on the affected side The typical cleft in syringobulbia is so placed as to interfere with connections between the vestibular nuclei and medial longitudinal fasciculus and between the descending nucleus and tract of the trigeminal nerve and the trigeminothalamic pathways thus nystagmus and sensory impairment on the face (with loss of the corneal reflex) generally result The lesion also may involve the hypoglossal fibers and the nucleus ambiguus of the vagus thereby giving rise to atrophy of one side of the tongue and unilateral palatal and vocal cord paralysis Kyphoscoliosis is an almost universal feature of syringomyelia The mechanism appears to be an unequal atrophic paralysis of paravertebral muscles It may precede the other neurologic abnormalities by many years The impaired sensation and interference with autonomic innervation frequently are associated with trophic changes in the affected segments—such as edema and cyanosis of the hands ulcerations of the skin and painless destruction of joints reproducing the Charcot joints of tabes dorsalis Occasionally the disease appears in childhood but usually the clinical manifestations do not become apparent until young adult life It is slowly progressive but not always steadily so and there may be long periods of arrest or even slight remission

Differential Diagnosis This is not difficult in typical and well advanced cases but the possibility of spinal cord tumor must always be kept in mind when the syringomyelic syndrome is encountered and steps must be taken to rule it out Other compressive lesions inflammatory or traumatic likewise must be excluded The suspicion of syringomyelia may at times be strengthened by the roentgenographic finding of widening of the interpedicular spaces of the cervical vertebrae but this merely indicates the presence of a chronic enlargement of the cord and does not disclose its nature Multiple sclerosis may at times produce similar sensory changes but almost never causes weakness of lower motor neurone type Conversely motor system disease which can produce motor abnormalities resembling those of syringomyelia never results in detectable sensory changes

Treatment On the theory that the cavitation may result from an intrinsic and independent proliferation of the glia (with breakdown in the center of the gliosis to form the syrinx) x ray therapy has been used for many years in attempts to treat syringomyelia Although some patients appear to benefit from this the results are generally disappointing Nevertheless radiation in small amounts under the guidance of an expert roentgenologist, may be warranted in selected cases In those cases in which the syrinx becomes distended with fluid in subarachnoid block, laminectomy and drainage of the cavity may produce considerable benefit On the whole however there is no satisfactory form of treatment for these cases

Progressive Neural Muscular Atrophy

The remaining group of degenerative disorders characterized by progressive weakness and wasting of skeletal muscles combined with sensory changes are chronic diseases of peripheral nerves often occurring as hereditary conditions Although clinical and pathologic subvarieties exist there is no sharp dividing line between them and they are best considered together under the designation given above in which the term *neural* emphasizes the peripheral nerve affection As already pointed out above chronic peripheral neuropathy is an associated disorder in some of the hereditary ataxias and is regularly encountered in the classic form of Friedreich's ataxia An additional connecting link with other genetically determined nervous diseases is the occurrence of progressive optic atrophy or pigmentary degeneration of the retina in some cases Common to all is for the neuropathy to begin distally and to progress in a centripetal fashion and for the feet and legs to become first affected with involvement of the hands and more proximal parts only after a considerable interval

The variety most usually seen is that generally called *peroneal muscular atrophy* (Charcot Marie Tooth disease) which draws attention to the changes in the lower legs although the disorder affects far more than the peroneal muscle groups or nerves Although it had been previously described it was first clearly differentiated from other forms of muscular atrophy by Charcot and Marie in France and independently by H H Tooth in England in 1886 In rare cases which are otherwise similar there is a remarkable palpable thickening of peripheral nerve trunks Such cases are generally designated *hypertrophic interstitial neuropathy* (of Dejerine and Sottas after the French neurologists who in 1893 first described the condition clinically and pathologically) In a few cases there are pronounced trophic and vasomotor abnormalities of the affected parts chiefly the feet which may lead to chronic poorly healing perforating ulcers on the ball of the foot among other abnormalities (*familial neurovascular dystrophy* Wadulla 1949 Krucke 1955 *hereditary sensory neuropathy* Denny Brown 1951) Probably related is the unusual condition

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260 DISEASES OF THE PERIPHERAL NERVES

Vincent Perlo and Raymond D Adams

Definition According to common clinical usage multiple symmetric involvement of peripheral nerves resulting in varying degrees of muscular weakness and sensory impairment is termed *polyneuritis* *Mononeuritis* indicates involvement of single nerves *Neuritis* implies inflammatory disease of nerves but inflammatory reactions in the neuritides are uncommon compared with the incidence of toxic metabolic or ischemic processes The terms *neuropathy polyneuropathy* and *mononeuropathy* are considered preferable in describing noninflammatory conditions

General Considerations The peripheral nervous system includes 12 pairs of cranial nerves originating from the brain and 31 pairs of segmentally arranged spinal nerves arising from the spinal cord The parts of the spinal nerves within the spinal canal and attached to the ventral and dorsal surfaces of the cord are called *roots* The dorsal roots contain afferent fibers of which the cells of origin are in the dorsal root ganglions while ventral root fibers arise from anterior horn cells in the gray matter of the cord The dorsal and ventral roots join to form the spinal nerves just outside the intervertebral foramens Each spinal nerve receives fibers from the sympathetic trunk of its own side

The peripheral nerves are composed of myelinated and unmyelinated nerve fibers bound together by endoneural connective tissue Each fiber bundle is surrounded by a connective tissue sheath or perineurium and groups of bundles are enveloped by epineurium forming nerve trunks The nerve fibers or axones vary in size and in the number of myelinated fibers The myelinated fibers are surrounded by a sheath of myelin and this in turn is invested by a thin membranous neurilemma sheath The myelin sheaths are interrupted by nodes of Ranvier and each segment of myelin contains a single Schwann cell Motor fibers are generally large and myelinated while sensory branches are composed mainly of smaller myelinated and unmyelinated fibers Each nerve has its own vascular lymphatic and nerve supply Affection of single or multiple nerves or roots results in varying degrees of sensory loss motor weakness and autonomic disturbance depending on the severity of the lesion and the type of fibers involved

Pathologically the different diseases of the peripheral nerves have certain points in common Degeneration of medullated nerve fibers is found in all though it varies in degree and site of the primary damage The myelin sheaths are most susceptible The sheath disintegrates and forms ovoid masses or balls and often fine droplets These excite a reaction in the histiocytes which are converted into fatty macrophages as they phagocytize particles of myelin This myelin change may be limited to a few segments of the myelinated fiber a condition sometimes referred to as the *periaxial degeneration of Gombault* or the entire nerve distal to the point of damage may be affected (so-called *Wallerian degeneration*) The axis cylinders may swell, become granular and undergo fragmentation But as a rule axis cylinder damage is less pronounced than that of the myelin sheath

The location of the primary damage varies In acute idiopathic and diphtheritic polyneuritis the dorsal and ventral roots spinal ganglions and spinal nerves bear the brunt of the damage and the more peripheral parts of the nerve are affected only very slightly if at all In diabetic polyneuropathy ganglions root and proximal nerves are involved and this may extend secondarily to the spinal cord In alcoholic and arsenical polyneuropathy and many cases of porphyria the changes are mostly in the peripheral segments of the nerves Very commonly the axis cylinders are affected relatively little in comparison with the myelin sheaths The degeneration of dorsal root ganglion cells occurs in only a few types of polyneuritis such as diabetic idiopathic and diphtheritic polyneuritis When the ganglion cell is destroyed there is invariably a degeneration of the axis cylinder and myelin sheath in the peripheral nerve dorsal root and posterior columns of the spinal cord Whenever the motor nerve fibers degenerate the anterior horn cells within the spinal cord swell and undergo chromatolysis (axonal reaction)

The various types of polyneuritis are distinguished then by the character and extent of the nerve fiber changes However certain other pathologic changes also serve to differentiate them In idiopathic polyneuritis there is an infiltration of inflammatory cells i e lymphocytes plasma cells and mononuclears in the roots spinal ganglions and nerves In polyarteritis nodosa not only is the nerve degeneration distributed in foci according to the location of vascular occlusion but there is a unique necrotizing panarteritis Amyloid neuritis is identified by the deposits of material staining like amyloid in the intraneural blood vessels and connective tissue

The pathogenesis of diseases of the peripheral

Differential Diagnosis Multiple sclerosis may at times act in a manner identical to that just described but without a definite hereditary background and with a much better outlook for improvement of vision Toxic or nutritional amblyopia can generally be excluded by history and associated clinical findings In some cases it may be necessary to eliminate the possibility of a tumor compressing the chiasmal region and optic nerves although some evidence of bitemporal field defects would be then expected rather than bilateral central scotomas alone In addition to careful roentgenograms of the skull and cerebrospinal fluid examination pneumoencephalographic visualization of the chiasmal region may be indicated in case of serious doubt

Pigmentary Degeneration of the Retina (Retinitis Pigmentosa)

This may at times occur as a relatively independent disorder although it is often associated with other abnormalities of which cataracts deafness and mental deficiency are outstanding It is strongly hereditary chiefly as a recessive trait although dominant inheritance has been seen Pigmentary degeneration of the retina is one of the features of the Laurence Moon Biedl syndrome (Chap 28) It also accompanies some cases of neuronal lipoidosis or hereditary ataxia as already noted

Pathology The principal lesion is a degeneration of the rods and cones associated with displacement of melanin containing cells from the pigment epithelium into more superficial parts of the retina Other retinal structures are relatively intact

Clinical Aspects The disorder typically begins in childhood first as night blindness The visual fields become concentrically narrowed from the periphery to the center until eventually (by adolescence or perhaps not until middle age) very little useful vision remains Ophthalmoscopic examination may be normal at first but generally discloses irregular patches of dark pigment in the periphery of the retina When cataracts are likewise present as sometimes is the case visual acuity may be significantly improved by their removal The frequent association of the retinal lesions with other abnormalities has been mentioned in previous paragraphs

Differential Diagnosis Chorioretinitis from other causes (e g syphilis) may present a similar ophthalmoscopic appearance and should be excluded The hereditary background and the progressive course with night blindness and peripheral constriction of the visual fields may lead to the diagnosis even in the rare cases where pigmentary deposits in the retina are absent In most instances the opinion of a qualified ophthalmologist must be obtained

CONCLUSION

An attempt has been made to summarize information about some of the most important of the large group of the degenerative diseases of the nervous system Although there have of necessity been some omissions it is hoped that this chapter may serve as a guide to what may seem to be an impenetrable maze of eponyms and overlapping syndromes

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Paralysis of the external ocular muscles may occur in exceptional cases

The tendon reflexes are occasionally retained in the early stages of polyneuropathy but by the time sensory and motor paralysis has developed they are nearly always lost Reflex loss may be restricted to the legs—absent knee and ankle jerks —or there may be generalized areflexia Cutaneous reflexes i e abdominal and plantar are not affected

In certain cases vasomotor changes in the skin occur These include excessive sweating mottling cyanosis and edema Vasomotor paralysis resulting in hot dry skin is less frequently observed In chronic forms of polyneuropathy postural syncope may occur as a consequence of this vasomotor paralysis

CLINICAL VARIETIES OF POLYNEUROPATHY

Acute Polyneuritis

Acute Idiopathic Polyneuritis Acute idiopathic polyneuritis (infectious polyneuritis Landry s paralysis Guillain Barré syndrome acute polyneuritis with facial diplegia polyradiculoneuritis) is confined to the peripheral nervous system and is usually characterized by symmetric ascending motor weakness areflexia distal sensory impairment and albuminocytologic dissociation of the spinal fluid The various designations given above are felt to be different names for the same condition first described by Landry in 1859 Although the clinical picture may vary considerably the pathologic changes are relatively constant When death occurs a week or more following the onset of symptoms there is marked degeneration of spinal nerves roots and ganglions with infiltration of inflammatory cells There is no evidence that the process extends to the central nervous system In view of the acute nature of the disease and the inflammatory character of the lesions an infectious etiology has been assumed but no evidence of virus or other infectious agent has been demonstrated

The condition usually begins within a week or two following an acute febrile illness most commonly an upper respiratory infection In some cases there is no history of prior illness Initial symptoms usually develop rapidly symmetric weakness of the lower extremities is accompanied by paresthesias in the fingers and toes Over a period of several days to a week weakness may progress to involve the trunk upper extremities face and bulbar muscles In the extremities both the distal and the proximal muscle groups are involved However the degree of weakness is variable at times reaching almost total voluntary paralysis Although the lower extremities tend to be involved first followed by upward spread of paralysis occasionally the arms or the muscles supplied by cranial nerves may be affected initially There is usually some impairment of position and vibratory sensation in the toes and fingers with relative sparing of other sensory modalities Pain is usually not a prominent symptom but in some cases it may be conspicuous and there may be tenderness of muscles and nerve trunks The muscles become flaccid and the tendon reflexes disappear as weakness increases Sphincter impairment is uncommon but transitory urinary retention may occur The motor weakness reaches a peak and remains unchanged for days or weeks If the patient survives the initial acute phase the prognosis for recovery is good and improvement once started usually progresses rapidly although occasionally convalescence may be prolonged During the acute phase mortality due to respiratory and vasomotor paralysis is as high as 30 per cent A characteristic finding in the spinal fluid is an elevated protein with a normal cell count (albuminocytologic dissociation) This spinal fluid formula appears in most cases but occasionally the protein is not elevated and rarely there is a significant number of lymphocytic cells in the spinal fluid There is usually a moderate polymorphonuclear leukocytosis in the peripheral blood

Acute idiopathic polyneuritis must be distinguished from other acute affections of peripheral nerves and roots poliomyelitis and acute ascending myelitis Postdiphtheritic polyneuritis produces a somewhat similar picture and may be identified by the recent history of diphtheria and transitory paralysis of palate or accommodation A positive Schick test is evidence against a preceding diphtheritic infection Acute porphyric polyneuropathy is distinguished by a recent history of abdominal symptoms normal spinal fluid protein and presence of porphyrins in the urine In acute idiopathic polyneuritis the features of acute onset following a febrile episode the rapid development of symptoms and the more prominent involvement of motor nerve fibers can help distinguish it from deficiency and toxic forms of polyneuropathy Meningeal carcinomatosis with multiple involvement of nerve roots is characterized by less acute onset steady progression of symptoms and frequently by inflammatory and neoplastic cells in the spinal fluid Poliomyelitis is distinguished by the asymmetric paralysis absence of sensory impairment and by the pleocytosis of the cerebrospinal fluid Acute ascending myelitis may cause widespread flaccid paralysis but in this condition sphincter disturbance is usually severe sensory loss is more extensive involving the whole body below the level of the cord lesion and plantar responses are later extensor

nervous system is largely unexplored In some diseases the primary disorder appears to be a direct affection of Schwann cells and the myelin sheath segments which they control (diphtheria toxin) In others the sensory and motor nerve cells are involved and changes in the myelin sheath may be secondary (beriberi?) Inflammatory or other alterations in the connective tissues of the nerves may be the mechanism of another type of peripheral neuropathy (lupus erythematosus?) Ischemia resulting from occlusion of the nutrient arteries e g polyarteritis nodosa is still another mode of nerve fiber damage Stretch laceration compression and other mechanical factors are operative in injuries of peripheral nerves

There is often a remarkable discrepancy between the degree of functional impairment before death and the degree of nerve fiber degeneration at autopsy particularly in the acute cases With complete paralysis there may be degeneration of only a few fibers or nearly every one may be involved This fact undoubtedly explains differences in the recovery rate from acute polyneuropathy

CLASSIFICATION

PRINCIPAL CAUSES OF PERIPHERAL NEUROPATHY

I Polyneuropathy (generalized neuropathy)
- A Poisons
  1. Metals arsenic lead mercury antimony bismuth copper phosphorus thallium
  2. Organic substances carbon monoxide carbon disulfide trichloroethylene methyl alcohol triorthocresylphosphate immune serums benzene and derivatives
- B Deficiency states and metabolic disorders chronic alcoholism beriberi pellagra combined system disease pregnancy chronic gastrointestinal disease carcinoma of lung diabetes mellitus porphyria amyloid disease
- C Infections
  1. Acute idiopathic polyneuritis (acute febrile polyneuritis of Osler Landry Guillain Barre syndrome)
  2. Polyneuropathy complicating acute or chronic infection diphtheria Boeck s sarcoid infectious mononucleosis
  3. Local infection of nerves leprosy
- D Vascular disease polyarteritis nodosa arteriosclerosis
- E Familial polyneuropathy progressive hypertrophic polyneuropathy peroneal muscular atrophy
- F Polyneuropathy of obscure origin chronic progressive or recurrent polyneuropathy

II Mononeuropathy (localized neuropathy)
- A Infections diphtheria leprosy herpes zoster sarcoid local sepsis
- B Trauma including stretching laceration and contusion external pressure compression by tumor herniated disk or cervical rib injection of medication into nerve
- C Tumors neurofibroma neurofibrosarcoma von Recklinghausen s neurofibromatosis
- D Idiopathic Bell s palsy brachial and sciatic neuritis
- E Serum neuritis
- F Vascular disease polyarteritis nodosa

GENERAL SYMPTOMS AND SIGNS OF POLYNEUROPATHY

Multiple peripheral nerve involvement is characterized by varying degrees of symmetric or asymmetric sensory impairment and motor weakness as a rule most pronounced over the distal portions of the extremities

Numbness and tingling of the hands and feet are frequent subjective symptoms They are variously described as prickling formication and "sleepy feeling in medical terminology they are called *paresthesias* They nearly always indicate involvement of fibers which convey the senses of touch vibration and position and impairment of these sensory modalities is usually found The skin may be exquisitely tender to touch pressure and pricking or pinching which produce a disagreeable sensation (dysesthesia) lasting for some time after the removal of the stimulus Marked tenderness to palpation over nerve trunks or muscles is common There may be hyperpathia or excessive reaction with raised threshold to painful stimulation and persistence of severe discomfort after removal of the stimulus Some degree of objective sensory impairment in the extremities is usually present Perception of light touch and pain is characteristically impaired in a distal distribution sometimes referred to as glove and stocking but is unlike hysterical sensory loss in that there is a gradual change to normal sensation proximally Position and vibratory sensation are diminished in the toes and fingers to varying degrees and these changes underlie the sensory ataxia and stereoanesthesia commonly observed with involvement of these modalities Impairment of temperature sensation frequently occurs and heat or cold may produce altered disagreeable sensations i e burning painful coldness (thermal dysesthesias)

Muscular weakness varies from slight involvement of distal muscle groups to complete symmetric paralysis of all muscles in the extremities and face In milder forms of weakness foot and wrist drop are common Muscle groups involved become flabby and undergo atrophy fairly rapidly Of the muscles innervated by cranial nerves bilateral facial involvement is most frequent followed by paralysis of bulbar muscles i e tongue pharynx larynx

The arms are infrequently involved The reflexes in the legs are sluggish or absent The spinal fluid protein is frequently elevated without increase in the cell count There is rarely a generalized polyneuropathy involving all extremities and producing symmetric atrophy weakness and sensory impairment A mononeuritic form of diabetic neuropathy may occur in which single nerve trunks are involved e g sciatic or femoral with symptoms referable to the distribution of the involved nerve Involvement of autonomic nerves occurs occasionally resulting in the loss of sweating impaired vasomotor control dependent edema gastrointestinal disturbance and sphincter impairment Cranial nerve lesions may occur unilateral third or sixth nerve palsy being most frequent but this is nearly always an isolated phenomenon unrelated to peripheral neuropathy The pathogenesis is unknown Vitamin deficiency or the vascular changes of Kimmelstiel Wilson disease have been suggested as the basis of the pathologic changes but are unproved The prognosis for improvement of diabetic neuropathy is usually good Treatment consists in rigid control of the diabetes with maintenance of relatively normal levels of blood sugar Vitamin supplements of the B group are usually added Pregnant mammalian liver extract has been ineffective in the experience of the authors

Porphyric Polyneuropathy Acute porphyria is characterized by the sudden development of abdominal cramps vomiting constipation fever tachycardia hypertension and leukocytosis During the height of these symptoms the urine changes to a burgundy color on exposure to light this is at least partly because of the conversion of porphobilinogen to uroporphyrin Toxic delirium and convulsions may occur during the phase of abdominal symptoms Many patients have recurrent attacks of abdominal pain without neurologic manifestations Shortly after the abdominal crisis signs of polyneuropathy may appear with rapidly developing flaccid paralysis of the legs and arms extending at times to involve the bulbar muscles Pains and paresthesias in the extremities are common and there is often objective sensory impairment Uroporphyrin is present in the urine and can be demonstrated by a pinkish fluorescence under ultraviolet light The presence of urinary porphobilinogen can be demonstrated by the Watson test The mortality in cases of polyneuropathy in porphyria is as high as 50 per cent and is due to bulbar or respiratory paralysis The involved nerves demonstrate acute degenerative lesions with little interstitial reaction Treatment is limited to symptomatic measures although cortisone or ACTH may be of value Barbiturates are contraindicated and other drugs should be used cautiously to avoid accentuation of symptoms

Amyloid Polyneuropathy Primary amyloidosis is a rare condition in which amyloid is deposited in blood vessels connective tissue and (rarely) in nerves A clinical picture of slowly progressive sensorimotor polyneuropathy is produced which may resemble beriberi or hypertrophic polyneuropathy Electrocardiographic changes and anemia are found in some patients The diagnosis is established by finding amyloid in a biopsy of skin and muscle Many of these cases have a plasmocytoma or multiple myeloma The clinical picture must be distinguished from that of a toxic polyneuropathy due to stilbamidine treatment or a compression myelopathy (myelomatous paraplegia)

Vascular Disease

Polyneuropathy Associated with Periarteritis Nodosa Multiple ischemic involvement of peripheral nerves secondary to damage to nutrient arteries occurs frequently in periarteritis nodosa Occasionally only single nerves may be involved resulting in mononeuropathy with sensory and motor symptoms restricted to the distribution of the damaged nerve Usually the nerves are involved diffusely and produce a clinical picture of subacute polyneuropathy with pain muscular wasting areflexia and peripheral sensory impairment Although at times symmetric in distribution its most distinctive features are its asymmetry and its intermittently progressive course The neurologic manifestations occur in association with the usual syndrome of fever cachexia hypertension abdominal pain focal visceral symptoms and eosinophilia See Chap 262 for treatment

Poisons

Arsenical Polyneuropathy Polyneuropathy resulting from chronic arsenical poisoning is relatively infrequent The involved nerves show nonspecific degenerative changes The symptoms develop rather slowly and are of both sensory and motor type like those of alcoholic polyneuropathy Pain and paresthesias in the legs and feet are prominent Weakness in the lower extremities is more pronounced than in the upper ones Disturbance of the mental functions convulsions and coma due to arsenical encephalopathy may occur The subacute course of the illness in conjunction with certain other findings is of importance in diagnosis These other findings include gastrointestinal irritation brownish cutaneous pigmentation most marked about normally pigmented areas hyperkeratosis of the palms and soles and white transverse bands in the nails (Mees lines) anemia and signs of liver disease The diagnosis is confirmed by demonstration of arsenic in the hair nails urine or feces Treatment consists of withdrawal from exposure and administration of BAL in doses of 3 mg per kg body

The treatment is symptomatic with the use of the respirator in the acute phase if respiratory paralysis occurs Adrenal steroids have been used in a few cases with encouraging results but have had no effect in others A trial of these hormones is indicated in critically ill patients in a dosage of 300 mg per day for 2 days and 150 mg daily thereafter for at least 2 to 3 weeks (Meticorten 25 to 30 mg per day)

Diptheritic Polyneuritis In the course of diphtheria various localized neuritic manifestations occur early in the disease and may be followed by the later development of generalized polyneuritis with degenerative changes in the spinal ganglions roots and peripheral nerves These complications occur more frequently in children than in adults Palatal paralysis occurs during the second or third week and occasionally earlier It is characterized by nasal speech and regurgitation of fluids through the nose Paralysis of accommodation with inability to focus on near objects may occur at the same time During the fifth to seventh weeks of the illness generalized sensorimotor polyneuritis develops but it may be delayed up to 2 or 3 months from the onset of diphtheria It may occur without evidence of a preceding pharyngitis or localized neuritis The progression and course of diphtheritic polyneuritis are similar in many respects to those of idiopathic polyneuritis and clinically it may be difficult to distinguish between the two conditions The generalized symptoms and signs progress for a week or two then become stationary and gradually subside The lower limbs tend to be more involved than the upper and distal muscle weakness is more pronounced than proximal Paresthesias in the fingers and toes are prominent and sensory impairment conforms to a distal distribution Position sense is often greatly impaired The tendon reflexes disappear The spinal fluid protein is usually elevated and always without increase in cells Improvement usually begins within a few weeks but may be delayed for months Prognosis for complete recovery is usually good Fatalities have usually been due to myocarditis or respiratory paralysis Treatment is symptomatic Administration of antitoxin is of no value once paralysis has developed Antitoxin given within several days of the onset of diphtheria usually prevents the development of polyneuritis

Pink Disease (Erythredema Polyneuropathy) This syndrome of obscure etiology occurs in young children and is characterized by chronic polyneuropathy with generalized weakness muscular hypotonia areflexia and distal sensory impairment Typical associated findings are swelling and erythema of the face hands trunk and feet irritability insomnia anorexia alopecia and trophic changes of the skin Fever is usually absent The peripheral nerves show degenerative changes Improvement occurs slowly over a period of months Treatment is symptomatic with vitamin supplements on the assumption that the condition may represent a deficiency disease A similar clinical picture has been produced by mercury intoxication in children In some of these cases rapid improvement resulted following administration of BAL

Leprous Polyneuritis In leprosy there is marked irregular thickening of peripheral nerves owing to formation of leprous nodules i e aggregations of inflammatory cells and Hansen bacilli surrounded by a connective tissue capsule Secondary degeneration of myelin and axones occurs Multiple peripheral nerves are involved producing symmetric distal weakness and sensory impairment Leprous nodules in the skin of the face are common and in many cases there is facial anesthesia Trophic changes with necrosis of phalanges are observed in some patients The greatly thickened nodular nerves are frequently palpable The diagnosis can be proved by demonstrating bacilli in nasal scrapings or by biopsy of a leprous nodule

Deficiency and Metabolic Disorders

Alcoholic Polyneuropathy This is described in Chap 99 Alcohol Other conditions caused by thiamine deficiency are beriberi polyneuropathy of pregnancy and chronic deficiency syndromes due to gastrointestinal disease The symptoms of polyneuropathy in these conditions are similar to those encountered in the alcoholic variety

Polyneuropathy due to degeneration of peripheral nerves occurs also in pellagra and is said to occur in combined system disease The latter responds to administration of liver extract or vitamin B_1

Recently cases of sensory and sensorimotor polyneuropathy have been discovered in association with bronchogenic carcinoma and multiple myeloma The mechanism of the neuropathy in these conditions is obscure

Diabetic Polyneuropathy About 50 per cent of older diabetic patients have a mild and relatively asymptomatic neuropathy with absent ankle jerks and impaired vibratory sensation in the toes as the only signs Symptomatic neuropathy on the other hand occurs in about 4 per cent of diabetic patients and is more frequent among patients with poorly controlled diabetes i e prolonged hyperglycemia and weight loss There are burning tearing or lancinating pains in the calves and paresthesias in the feet The pains occur frequently during the night Motor weakness is not prominent in some cases but dominates the clinical picture in others (diabetic amyotrophy) Sensory impairment involves mainly pain with only slight loss of touch and pressure sensation Occasionally vibratory and position senses alone may be impaired (diabetic tabes)

DIAGNOSIS OF POLYNEUROPATHY

In the differential diagnosis the first problem is to determine whether the disease is spinal muscular or neural The characteristic symmetric involvement of the extremities muscle and nerve tenderness distal sensory impairment areflexia, muscle atrophy trophic skin changes and absence of sphincter impairment are distinguishing features of polyneuropathy Pain ataxia and loss of reflexes in the lower limbs occur in tabes but unlike polyneuropathy there is no motor paralysis muscle tenderness or atrophy and lightning pains Argyll Robertson pupils bladder disturbances and serologic tests set it apart

Poliomyelitis is distinguished by the absence of objective sensory disturbance and by the presence of segmental rather than peripheral distribution of muscle paralysis asymmetry of paralysis evidence of meningeal irritation and spinal fluid pleocytosis *Trichinosis* may simulate polyneuropathy because of muscle tenderness and weakness but is distinguished by the periorbital edema preservation of tendon reflexes absence of sensory impairment and the presence of eosinophilia *Dermatomyositis* may be associated with pronounced muscle weakness but the weakness is usually proximal, there is no sensory impairment and the tendon reflexes are often preserved *A distal form* of myopathy may resemble chronic motor neuropathy and in some instances the differential diagnosis must depend on biopsy Many of the myopathic cases are familial *Acute myelitis* causes rapidly developing symmetric paralysis with sensory loss but may be distinguished from polyneuropathy by the presence of extensor plantar responses sensory impairment involving the whole body below the level of the lesion and severe sphincter disturbance Once the diagnosis of polyneuropathy is made the particular type must be determined by reference to the clinical features described above

LOCALIZED NEUROPATHY

The Common Brachial and Crural Mononeuropathies

Brachial Palsies The fifth to eighth cervical and first thoracic spinal nerves innervate the muscles of the shoulder girdles and upper extremities The brachial plexus is formed by components of these nerves and lesions of the nerves or their branches result in characteristic palsies The following are the brachial palsies most likely to be observed on the medical wards of a hospital

Long Thoracic Nerve This nerve is derived from the fifth sixth and seventh cervical nerves and supplies the serratus magnus muscle Paralysis of the serratus magnus muscle results in inability to raise the arm over the head from a forward position and there is winging of the inner border of the scapula on pushing forward against resistance It is injured most commonly by pressure on the shoulder from either a sudden blow or prolonged pressure from carrying heavy weights It is also involved at times in diabetic patients and as a manifestation of brachial or serum neuritis

Suprascapular Nerve This nerve is derived from the fifth and sixth cervical nerves and supplies the supra and infraspinatus muscles Lesions may be diagnosed from the presence of weakness of abduction and external rotation of the arm and atrophy of the supra and infraspinatus muscles The nerve may be injured by blows on top of the shoulder and fracture-dislocations of the shoulder joint.

Upper Brachial Plexus Paralysis This is due to injury to the fifth cervical nerve caused most commonly by forceful separation of the head and shoulder during difficult delivery or by pressure in the supraclavicular region during anesthesia. The muscles affected are the biceps deltoid brachialis anticus supinator longus supra and infraspinatus and rhomboids The arm hangs at the side internally rotated with the elbow extended The forearm is pronated Hand motion is unaffected The prognosis for spontaneous recovery is generally good especially in cases of birth injury This condition as a result of birth injury (Erb-Duchenne brachial plexus palsy) is discussed in Chaps 25 and 253

Lower Brachial Plexus Paralysis This is due to injury to the eighth cervical and first thoracic roots as a result of traction on the abducted arm in falls during operation and with tumors of the apex of the lung (superior sulcus or Pancoast syndrome) Injury may occur during birth (Dejerine-Klumpke brachial plexus injury) There are paralysis and wasting of the small muscles of the hand and a characteristic claw hand deformity Sensory loss is limited to the ulnar border of the hand and there may be an associated paralysis of the cervical sympathetic nerve with a Horner's syndrome

Lesions of the Cords of the Brachial Plexus The outer and inner cords are most commonly affected Dislocation of the head of the humerus pressure of the cervical rib and stab wounds are the most frequent causes Injury to the outer cord results in paralysis of the biceps and coracobrachialis muscles and all muscles supplied by the median nerve except the intrinsic hand muscles There is some loss of sensation over the radial aspect of the forearm Involvement of the inner cord as may occur in compression by cervical rib results in paralysis of the muscles supplied by the ulnar nerve together with the median innervated intrinsic muscles of the

weight every 4 to 6 hr for 3 days and then twice daily for 10 days The prognosis is usually good but depends on the duration of symptoms prior to treatment Recovery of motor power may require months or a year or more

Poisoning due to mercury thallium and antimony may also cause a polyneuropathy which may respond to the administration of BAL

Lead Neuropathy Lead neuropathy occurs following chronic exposure to lead and its most characteristic feature is the predominantly motor affection involving mainly the upper extremities The radial nerves are most frequently involved producing wrist and finger drop without sensory manifestations Less commonly weakness of proximal shoulder girdle muscle occurs and in the lower extremities foot drop may appear Clinically the paralyzed muscles are those which are most used Important associated findings are anemia basophilic stippling of red blood cells lead line along the gingival margins colicky abdominal pain and constipation Neuropathy occurs usually in adults and is infrequent in children In contrast lead encephalopathy manifested by increased intracranial pressure convulsions blindness and coma occurs more frequently in children The diagnosis of lead neuropathy is established by the history of lead intoxication the characteristic motor involvement associated findings and increased urinary excretion of lead Treatment consists of withdrawal from exposure to lead and measures to eliminate lead from the blood stream (see p 765) The prognosis for recovery of motor power is good although in chronic cases recovery may be slow (see p 766)

Triorthocresylphosphate Polyneuropathy (Jamaica Ginger Paralysis) Periodic outbreaks of *polyneuropathy have occurred because of ingestion* of triorthocresylphosphate The largest number of cases occurred in 1930 following consumption of adulterated extract of ginger Recent cases have occurred because of the contamination of cooking oil Pathologically there are degeneration of peripheral nerves and also destruction of white matter and anterior horn cells in the spinal cord The initial symptomatology is that of gastrointestinal irritation followed in about 10 days by the development of a severe motor neuropathy involving distal muscles Wrist and foot drop occur Pain is common but there is usually no sensory impairment Later extensor plantar reflexes appear In many cases the paralysis fails to improve The treatment is symptomatic

Familial Polyneuropathy

Peroneal Muscular Atrophy (Charcot Marie Tooth Disease) This is a hereditary disease with onset during adolescence or adult years There is chronic degeneration of peripheral nerves and roots resulting in distal muscle atrophy beginning in the feet and legs and later in the hands Early symptoms are muscular wasting and weakness affecting the extensor and abductor muscles of the feet and producing an equinovarus deformity Later all muscles below the middle third of the thigh may be affected resulting in a stork leg" appearance of the legs After a period of years atrophy of hand and forearm muscles develops The wasting never extends above the elbows or above the middle third of the thighs Perforating ulcers may occur in the feet Pain paresthesias and cramps are common The sensory disorder is usually rather slight Often there is some impairment of position and vibratory sensation in the feet and touch and pain sensation are lost in the feet in some cases Reflexes are lost in the involved limbs The progression of the illness is very slow and may be arrested at any stage (See Chap 259 for more complete description)

Progressive Hypertrophic Polyneuropathy (Dejerine Sottas Disease) This type of neuropathy is uncommon and is frequently familial It begins usually in childhood and is slowly progressive Pain and paresthesias in the feet are early symptoms followed by development of symmetric weakness and wasting of the distal portion of the limbs Sensation is impaired in a distal distribution and the tendon reflexes are absent Miotic pupils nystagmus and kyphoscoliosis have been observed in some cases A characteristic finding is the enlargement of the peripheral nerves because of hypertrophy and proliferation of the cells of the sheath of Schwann and fibroblasts Palpable thickening of the ulnar and peroneal nerves may be conspicuous *In the absence of palpable enlargement* of nerves the diagnosis can be established by biopsy of a cutaneous nerve The treatment is symptomatic

Polyneuropathy of Obscure Origin

Chronic Progressive Polyneuropathy Not infrequently one encounters patients with a slowly progressive polyneuropathy in whom no etiologic factor can be found There are weakness and wasting of the limbs areflexia and peripheral sensory impairment Pain is less prominent than in the acute forms of neuropathy and is often absent altogether Progression occurs over a period of months occasionally with fatal termination but may be followed by recovery or arrest of the condition The peripheral nerves show evidence of widespread degeneration Without knowledge of etiology and lacking a specific therapy one can only resort to the usual symptomatic treatment of polyneuropathy A course of BAL may be tried on empirical grounds

Femoral Nerve This nerve is derived from the second third and fourth lumbar nerves It supplies the iliacus pectineus sartorius and quadriceps muscles and carries sensory impulses from the anteromedial aspect of the thigh and medial side of the lower leg Following injury to the nerve there is paralysis of extension of the knee with wasting of the quadriceps muscle and also some weakness of hip flexion The knee jerk is abolished The nerve may be involved in fractures and dislocation of the hip and in fractured pelvis It may be affected in diabetes polyarteritis nodosa and in retroperitoneal pelvic or abdominal lesions such as psoas abscess or tumor Because of the proximity of the femoral artery to the nerve in the femoral triangle wounds in this region may be fatal

Sciatic Nerve This nerve is derived from the fourth and fifth lumbar and first second and third sacral nerves It provides the motor innervation of the hamstring muscles and all those below the knee and it carries sensory impulses from the posterior aspect of the thigh and posterior and lateral aspects of the leg and entire sole In complete sciatic paralysis the knee cannot be flexed and all muscles below the knee are paralyzed The sciatic nerve is commonly injured in fractures of the pelvis or femur and in gunshot wounds of the buttock and thigh It may also be involved by pelvic tumors and in both diabetes mellitus and polyarteritis nodosa Cryptogenic forms also occur and are actually more frequent than the identifiable types of disease A ruptured lumbar disk often simulates sciatic neuropathy Incomplete lesions of the sciatic nerve occasionally result in causalgia

Common Peroneal Nerve This nerve is one of the terminal divisions of the sciatic nerve in the popliteal fossa It supplies the dorsiflexors of the foot and toes and everters of the foot, and sensation to the dorsum of the foot and lateral aspect of the lower half of the leg These functions are lost with lesions which completely interrupt the nerves Pressure or sleep palsy is one of the most frequent types of injury the compression being of that part of the nerve which passes over the head of the fibula It is also commonly involved by fractures involving the upper end of the fibula and in diabetic polyarteritis

Tibial Nerve This nerve is the other of the two terminal divisions of the sciatic nerve in the popliteal fossa It supplies all the calf muscles and the flexors of the foot Complete paralysis of the nerve results in a calcaneovalgus deformity of the foot which no longer can be plantar flexed There is loss of sensation over the plantar aspect of the foot

The Diseases Which Involve Single Nerves or Plexuses

Infections In faucial diphtheria selective involvement of the vagi and nerves to the ciliary muscles of the eye results in palatal paralysis and paralysis of accommodation The palatal palsy occurs in the first 2 weeks of infection and the loss of accommodation about a week later Both tend to improve rapidly In cutaneous diphtheria involvement of nerves locally results in paralysis of the muscles supplied by the spinal segment from which the infected region is innervated In leprosy granulomatous infection of multiple peripheral nerves usually takes place simultaneously producing symptoms of polyneuritis rather than localized asymmetric neuritis but the latter may be found in the early stages of leprous neuritis Herpes zoster is a sensory neuritis of virus etiology characterized by acute inflammation of one or more posterior root ganglions spinal nerves and roots and gray matter of the spinal cord Lancinating pain and hyperalgesia over the skin surface supplied by affected roots occur for 3 or 4 days followed by the appearance of a segmental herpetic eruption. If the inflammatory process spreads to involve adjacent motor roots of anterior horns of the cord segmental motor weakness and wasting appear Paralysis of the oculomotor nerves may occur in conjunction with involvement of the gasserian ganglion (ophthalmoplegic zoster) Facial paralysis may occur with involvement of the geniculate ganglion (Ramsay Hunt syndrome) but has accompanied zoster of other ganglions as well. Sarcoidosis can involve single or multiple peripheral nerves producing asymmetric mononeuritis or polyneuritis Unilateral or bilateral facial paralysis is common in association with parotitis and uveitis in sarcoidosis

Trauma External trauma may result in complete transection of a peripheral nerve or may impair conduction without interrupting the anatomic continuity of the involved nerve Complete division of a mixed peripheral nerve results in paralysis and sensory loss corresponding to the region supplied by the damaged nerve Recovery of function after complete division can take place only when the divided ends lie in apposition or have been sutured Growth of nerve fibers from the central end proceeds at a rate of 1 to 2 mm a day and the recovery time can be estimated by the distance between the site of injury and destination of the nerve An early indication of regeneration is the presence of tingling sensation on tapping the nerve below the lesion (Tinel's sign) Sensory recovery precedes the return of motor power All forms of cutaneous sensation begin to return together Appreciation of pain and temperature improves but the stimuli are poorly localized for some time Eventually there is recovery of the discriminative aspects of sensation, including localization of sensory stimuli, postural sense recognition of slight differences in temperature and appreciation of very light touch

hand and sensory loss over the ulnar aspect of the hand and forearm

Axillary Nerve This nerve arises from the posterior cord of the brachial plexus and supplies the teres minor and deltoid muscles It may be involved in injuries resulting from fractures of the neck of the humerus serum neuritis brachial neuritis or is part of a disease of unknown etiology The anatomic localization depends on the recognition of a paralysis of abduction of the arm wasting of the deltoid muscle and slight impairment of sensation over the outer aspect of the shoulder

Musculocutaneous Nerve This nerve is derived from the fifth and sixth cervical nerves and is a branch of the outer cord of the brachial plexus It innervates the biceps and brachialis anticus muscles Lesions of the nerve result in weakness of elbow flexion This nerve is rarely injured alone

Radial Nerve This nerve is derived from the fifth to eighth cervical nerves and is the termination of the posterior cord of the brachial plexus It innervates the triceps muscle and the supinator and extensor muscles of the forearm and hand Complete radial paralysis results in inability to extend the elbow paralysis of supination of the forearm and complete wrist and finger drop Sensation is impaired over the posterior aspect of the forearm and a small area over the radial aspect of the dorsum of the hand The nerve may be injured in the axilla for example in crutch palsy but is most commonly injured in the lower arm where the nerve winds around the humerus Common types of injury at this site are fractures and pressure palsies during sleep

Median Nerve This nerve is derived from the sixth cervical to the first thoracic nerves and is formed by the union of two heads from the inner and outer cords of the brachial plexus It innervates the pronators of the forearm long finger flexors and abductor and opponens muscles of the thumb and is a sensory nerve to the palmar aspect of the hand Complete median nerve paralysis results in wasting of the affected muscles and inability to pronate the forearm or deviate the hand in an ulnar direction paralysis of flexion of the index finger and terminal phalanx of the thumb weakness of flexion of the remaining fingers weakness of abduction and opposition of the thumb and sensory impairment over the radial two thirds of the palmar aspect of the hand and over the distal phalanges of the dorsum of the index and third fingers The nerve may be injured in the axilla by shoulder dislocation and at any part of its course by laceration stab or gunshot wounds The wrist is the most common site of external injury Compression of the nerve at the wrist (carpal tunnel syndrome) may occur secondary to prolonged occupational pressure or local infiltration for example by a thickening of connective tissue and deposit of amyloid with multiple myeloma Incomplete lesions of the median nerve between the axilla and wrist may result in *causalgia*

Ulnar Nerve This nerve is derived from the eighth cervical and first thoracic nerves It innervates the ulnar flexor of the wrist the inner half of the deep finger flexors the adductors and abductors of the fingers adductor of the thumb the two medial lumbricales and muscles of the hypothenar eminence It is the sensory nerve to the fifth and ulnar half of the fourth fingers and ulnar border of the hand Complete ulnar paralysis results in a characteristic claw hand deformity owing to wasting of the small hand muscles and hyperextension of the fingers at the metacarpophalangeal joints and flexion at the interphalangeal joints The flexion deformity is most pronounced in the fourth and fifth fingers Sensory loss occurs over the fifth finger the ulnar aspect of the fourth finger and the ulnar border of the palm The ulnar nerve is most commonly injured at the elbow because of fracture or dislocation involving the joint *Delayed ulnar palsy* may occur many years after an injury to the elbow joint which has resulted in a cubitus valgus deformity of the joint Because of the deformity the nerve is stretched in its course over the ulnar condyle The superficial location of the nerve at the elbow makes it a common site of pressure palsy Prolonged pressure on the outer part of the palm may result in damage to the deep palmar branch of the ulnar nerve causing weakness of small hand muscles but no sensory loss

Crural Palsies The twelfth thoracic first to fifth lumbar and first second and third sacral spinal nerve roots compose the lumbosacral plexuses and innervate the muscles of the lower extremities and saddle region The following are the common crural palsies

Lateral Femoral Cutaneous Nerve This nerve is derived from the second and third lumbar nerves It is a sensory nerve supplying the lateral aspect of the thigh The nerve enters the thigh beneath the lateral end of the inguinal ligament and then enters the fascia lata where it may become constricted Compression of the nerve results in uncomfortable paresthesias along its cutaneous distribution and in sensory impairment The condition is called *meralgia paresthetica* (mentioned below)

Obturator Nerve This nerve is derived from the second third and fourth lumbar nerves It supplies the adductor muscles of the thigh and injury to the nerve results in almost complete paralysis of adduction of the thigh The nerve is most frequently injured during the course of a difficult labor and also as a result of dislocation of the hip or an obturator hernia It may be affected in diabetes polyarteritis nodosa retroperitoneal cervical carcinoma and other tumors etc

Femoral Nerve This nerve is derived from the second third and fourth lumbar nerves It supplies the iliacus pectineus sartorius and quadriceps muscles and carries sensory impulses from the anteromedial aspect of the thigh and medial side of the lower leg Following injury to the nerve there is paralysis of extension of the knee with wasting of the quadriceps muscle and also some weakness of hip flexion The knee jerk is abolished The nerve may be involved in fractures and dislocation of the hip and in fractured pelvis It may be affected in diabetes polyarteritis nodosa and in retroperitoneal pelvic or abdominal lesions such as psoas abscess or tumor Because of the proximity of the femoral artery to the nerve in the femoral triangle wounds in this region may be fatal

Sciatic Nerve This nerve is derived from the fourth and fifth lumbar and first second and third sacral nerves It provides the motor innervation of the hamstring muscles and all those below the knee and it carries sensory impulses from the posterior aspect of the thigh and posterior and lateral aspects of the leg and entire sole In complete sciatic paralysis the knee cannot be flexed and all muscles below the knee are paralyzed The sciatic nerve is commonly injured in fractures of the pelvis or femur and in gunshot wounds of the buttock and thigh It may also be involved by pelvic tumors and in both diabetes mellitus and polyarteritis nodosa Cryptogenic forms also occur and are actually more frequent than the identifiable types of disease A ruptured lumbar disk often simulates sciatic neuropathy Incomplete lesions of the sciatic nerve occasionally result in causalgia

Common Peroneal Nerve This nerve is one of the terminal divisions of the sciatic nerve in the popliteal fossa It supplies the dorsiflexors of the foot and toes and everters of the foot and sensation to the dorsum of the foot and lateral aspect of the lower half of the leg These functions are lost with lesions which completely interrupt the nerves Pressure or sleep palsy is one of the most frequent types of injury the compression being of that part of the nerve which passes over the head of the fibula It is also commonly involved by fractures involving the upper end of the fibula and in diabetic polyarteritis

Tibial Nerve This nerve is the other of the two terminal divisions of the sciatic nerve in the popliteal fossa It supplies all the calf muscles and the flexors of the foot Complete paralysis of the nerve results in a calcaneovalgus deformity of the foot which no longer can be plantar flexed There is loss of sensation over the plantar aspect of the foot

The Diseases Which Involve Single Nerves or Plexuses

Infections In faucial diphtheria selective involvement of the vagi and nerves to the ciliary muscles of the eye results in palatal paralysis and paralysis of accommodation The palatal palsy occurs in the first 2 weeks of infection and the loss of accommodation about a week later Both tend to improve rapidly In cutaneous diphtheria involvement of nerves locally results in paralysis of the muscles supplied by the spinal segment from which the infected region is innervated In leprosy granulomatous infection of multiple peripheral nerves usually takes place simultaneously producing symptoms of polyneuritis rather than localized asymmetric neuritis but the latter may be found in the early stages of leprous neuritis Herpes zoster is a sensory neuritis of virus etiology characterized by acute inflammation of one or more posterior root ganglions spinal nerves and roots and gray matter of the spinal cord Lancinating pain and hyperalgesia over the skin surface supplied by affected roots occur for 3 or 4 days followed by the appearance of a segmental herpetic eruption If the inflammatory process spreads to involve adjacent motor roots of anterior horns of the cord segmental motor weakness and wasting appear Paralysis of the oculomotor nerves may occur in conjunction with involvement of the gasserian ganglion (ophthalmoplegic zoster) Facial paralysis may occur with involvement of the geniculate ganglion (Ramsay Hunt syndrome) but has accompanied zoster of other ganglions as well Sarcoidosis can involve single or multiple peripheral nerves producing asymmetric mononeuritis or polyneuritis Unilateral or bilateral facial paralysis is common in association with parotitis and uveitis in sarcoidosis

Trauma External trauma may result in complete transection of a peripheral nerve or may impair conduction without interrupting the anatomic continuity of the involved nerve Complete division of a mixed peripheral nerve results in paralysis and sensory loss corresponding to the region supplied by the damaged nerve Recovery of function after complete division can take place only when the divided ends lie in apposition or have been sutured Growth of nerve fibers from the central end proceeds at a rate of 1 to 2 mm a day and the recovery time can be estimated by the distance between the site of injury and destination of the nerve An early indication of regeneration is the presence of tingling sensation on tapping the nerve below the lesion (Tinel's sign) Sensory recovery precedes the return of motor power All forms of cutaneous sensation begin to return together Appreciation of pain and temperature improves but the stimuli are poorly localized for some time Eventually there is recovery of the discriminative aspects of sensation including localization of sensory stimuli postural sense recognition of slight differences in temperature and appreciation of very light touch

Pressure Palsy This results in temporary paralysis owing to local compression Mild degrees of compression are followed by fairly rapid recovery Severe compression such as may occur during a bout of alcoholic intoxication deep sleep or anesthesia may result in focal disintegration of myelin damage to axis cylinders and Wallerian degeneration of distal segments Recovery is slow and must await regeneration Common varieties of pressure palsy are radial nerve paralysis with wrist drop due to prolonged pressure against the back of the arm (Saturday night palsy) ulnar palsy due to repeated trauma to the nerve at the elbow especially after an old fracture that changes the relation of the nerve to the bicipital groove and peroneal nerve palsy with foot drop caused by compressing the nerve against the fibula as in sitting with legs crossed or during obstetric procedures with legs in stirrups

Meralgia paresthetica is a sensory neuropathy characterized by pain and paresthesia over the lateral aspect of the thigh because of compression of the lateral femoral cutaneous nerve in the fascia lata Pressure on nerve roots in the cervical and lumbar regions by *herniated intervertebral disks* results in pain sensory impairment and variable motor weakness corresponding to the area supplied by the involved root Compression of the inner cord of the brachial plexus by a *cervical rib or by some other malformation of the thoracic outlet* (thoracic outlet syndrome) results in atrophy of small hand muscles and sensory impairment over the ulnar and sometimes median nerve distribution The median nerve may be compressed at the wrist beneath the transverse carpal ligament (carpal tunnel syndrome) There are pain and paresthesias in the palmar surface of the hand and first three fingers thenar atrophy weakness in flexor of thumb and opponens muscle and sensory impairment over the median nerve distribution

Tumor Peripheral nerves may be compressed or invaded by primary or metastatic tumors arising in other tissues Solitary tumors of nerve sheaths or neuromas commonly occur along the roots of spinal nerves chiefly in the thoracic and lumbar regions Compression of the nerve root and adjacent spinal cord may occur Root compression causes pain referred to the distribution of the involved nerve and there may be associated sensory impairment and motor weakness Lymphomatosis and carcinomatosis of the cranial and spinal meninges may implicate single or multiple cranial and spinal nerve roots and give rise to confusing clinical syndromes Tumor cells may be found in the cerebrospinal fluid Solitary neuromas may involve any of the peripheral nerves producing local pain and tenderness to palpation Multiple neuromas occur in von Recklinghausen s disease and are associated in this condition with multiple congenital anomalies as well as kyphoscoliosis cutaneous pigmentation and cutaneous fibromas The treatment of solitary expanding nerve tumors of the limbs is wide excision with nerve graft or suture if that is possible

Idiopathic Neuropathy *Bell's palsy* is due to compression of the facial nerve in the fallopian canal as a result of an acute inflammatory process involving the nerve Edema leads to compression of nerve fibers with resulting unilateral paralysis of facial muscles (see p 267)

Brachial neuritis is an acute affection of the brachial plexus characterized by the acute or subacute onset of severe pain in the neck arm and hand followed by moderate muscle weakness slight impairment of sensation in the fingers and hand numbness or hyperesthesia and depressed reflexes in the involved arm The pain is usually severe and constant and is aggravated by moving the arm or stretching the brachial plexus Muscle wasting is rarely severe but some cases of brachial neuritis especially those described by the term *neuralgic amyotrophy* may be followed by localized paralysis and atrophy of the shoulder girdle and arm muscles Recovery slowly occurs over a period of several weeks to months Symptomatic treatment including complete rest of the involved arm and analgesics in the acute phase followed by mild massage and exercise usually suffices

Sciatic neuritis causes pain in the lumbar region and behind the leg from buttock to ankle The pain is aching or burning in quality and is aggravated by movement or straining The sciatic nerve is tender to palpation or stretching There may be slight weakness of the hamstrings and muscles below the knee The ankle jerk is absent Sensory impairment is usually slight It is necessary to distinguish the symptoms of sciatic neuritis from those of sciatic compression In compression (e g by tumor) the onset is more gradual symptoms are progressive muscle wasting is more conspicuous the nerve is less tender to palpation and sensory loss is greater The course of sciatic neuritis is stationary at first followed by slow improvement Treatment is symptomatic

Serum neuritis develops several days after the onset of serum sickness The fifth cervical nerve is most commonly involved with pain paralysis and atrophy corresponding to the distribution of the nerve Occasionally the entire brachial plexus may be involved and there is sometimes but rarely a generalized polyneuritis The etiology is not known but is attributed to perineural edema comparable to the urticaria of serum sickness with compression of affected roots or nerves Recovery is usually complete but occurs slowly

TREATMENT

In addition to measures already mentioned general principles in the treatment of polyneuropathy include removal of any known toxic factor correction of nutritional deficiency rest of affected nerves and muscles maintenance of muscle tone by heat massage and electrical stimulation and the prevention of joint fixation and contractures Bed rest is indicated for generalized weakness to relax involved muscles and to avoid cardiac strain Pain in the acute stage is relieved by analgesics and the use of moist hot packs if tolerated Pressure of bedclothes is avoided by cradle support and foot drop is prevented by sand bags beneath the soles Passive movement and gentle massage are started as soon as tolerated in order to maintain tone and prevent contracture After the acute painful stage appropriate splints can be worn and more intensive physiotherapy carried out Adequate nutrition must be maintained with vitamin supplements of the B group added In the nutritional polyneuropathies a high calorie high vitamin diet with 50 mg thiamine daily and 15 Gm of brewer's yeast t i d are prescribed On the basis of blood pyruvate levels following glucose administration it is said that three main groups of peripheral neuropathy can be distinguished One group shows no impairment of pyruvate metabolism and is not affected by thiamine treatment In the second group there is a block in pyruvate oxidation that responds to thiamine and in the third group a block in pyruvate oxidation that is not changed by thiamine The latter group includes cases of arsenic intoxication which respond to treatment with BAL In cases of polyneuropathy of obscure origin in which pyruvate metabolism is impaired if there is no response to thiamine a short trial of BAL is indicated The authors have been unable to verify this subdivision of cases of polyneuropathy and the efficacy of the therapeutic methods which follow from it has not been verified

Treatment in localized neuropathy is directed toward maintaining tone and preventing stretching of paralyzed muscles preventing contractures and keeping joints mobile while nerve regeneration is taking place Heat massage passive movement and electrical stimulation are employed Operative repair is necessary in cases of complete nerve transection and surgical treatment is required in some but by no means all cases of chronic compression by tumor cervical rib or herniated intervertebral disk

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Section 8 Diseases of Supporting Tissues Other Than Bone

Ivan L Bennett Jr

The next six chapters describe diseases that have in common the production of damage in the soft skeleton of the body the skin and connective tissues Although this categorization is somewhat arbitrary it possesses advantages Generally common or related etiology is the basis for classification and ideally similarity in manifestations is the most useful clinical criterion for grouping diseases Here we are dealing for the most part with diseases of obscure etiology many of the disorders are known

to occur in association with a variety of infections and hypersensitivity states Because injury to connective tissue can produce structural or functional abnormalities in almost any organ system or anatomic site *it is difficult to select a few predominant* symptoms and signs from the diversity of manifestations that can accompany such diseases and to rely on them is a logical starting point in grouping If they are considered by the clinician as generalized disorders of connective tissue however they are far less perplexing For example several genetically determined diseases once thought of as rare and esoteric syndromes composed of a peculiar hodgepodge of unrelated abnormalities are discussed in this section They are now known to be relatively common when viewed as disorders of connective tissue such associations as ectopia lentis inguinal hernia and dissecting aneurysm of the aorta in the Marfan syndrome or angioid streaks and melena in pseudoxanthoma elasticum are logical and expected

In addition to the major collagen vascular disorders several relatively unusual diseases of uncertain etiology that have closely related clinical or histologic manifestations are included polymyositis relapsing panniculitis and scleredema Because rheumatic fever and acute hemorrhagic nephritis are known to be related etiologically to group A streptococcal infection they are discussed in another part of the book as complications of streptococcal disease Both might well have been included in this section

The two most important afflictions of the joints rheumatoid arthritis and degenerative joint disease are included in this section along with a detailed discussion of the problem of arthritis Finally some of the fundamentals of clinical dermatology are presented from the point of view of the patient with skin disease or with systemic disease manifested by cutaneous lesions

261 HERITABLE DISORDERS OF CONNECTIVE TISSUE

Victor A McKusick

THE MARFAN SYNDROME

Definition The Marfan syndrome (synonyms arachnodactyly dolichostenomelia [long thin limbs] dystrophia mesodermalis congenita typus Marfanis etc) is a heritable generalized disorder of one element of connective tissue clinically manifested by abnormalities of the eye (especially ectopia lentis) of the skeletal system (especially excessive length of the long bones) and of the cardiovascular system (especially diffuse and/or dissecting aneurysm of the ascending aorta).

Clinical Manifestations *Skeleton* Characteristically the tubular bones are excessively long resulting in arachnodactyly and in anomalous proportions In the Marfan syndrome (Fig 199) the lower segment measurement (pubic symphysis to sole) which after puberty is normally about equal to the upper segment measurement is usually appreciably in excess of the upper segment measurement The arm span exceeds the height The patient with the Marfan syndrome is taller than the average for his age and family however the deviation from the normal skeletal proportion is of more specific diagnostic significance Excessive longitudinal growth of ribs may result in outward displacement of the sternum (pigeon breast pectus carinatum) or inward displacement (pectus excavatum *Trichterbrust*) Redundant ligaments tendons and joint capsules result in loose jointedness hyperextensibility of joints genu recurvatum (backward curvature of the legs at the knees) flat feet kyphoscoliosis and habitual dislocation of the hips patella clavicles mandible and other joints Hernia occurs with increased frequency In general patients with the Marfan syndrome display a sparsity of subcutaneous fat

Eye *Ectopia lentis* (subluxation of the lens dislocated lens) is the ocular hallmark of the Marfan syndrome Iridodonesis tremor of the iris is occasionally a clue to the presence of dislocated lenses Occasionally the margin of a dislocated lens is visible through the undilated pupil and occasionally there may be a total dislocation of the lens into the anterior chamber To exclude minor subluxation it is necessary to dilate the pupil maximally and perform a careful slit lamp examination Under these circumstances one sees in the severely affected person that the suspensory ligaments are redundant attenuated and fragmented

Myopia often of high grade is usually present a long orbit usually occurs as an integral part of the syndrome Spontaneous detachment of the retina is frequent

Cardiovascular System The principal cardiovascular manifestation of the Marfan syndrome *is a* weakness of the aortic media such that the portion subject to greatest hemodynamic stress of certain types—the ascending aorta—tends to undergo progressive dilatation or acute dissection The dilatation beginning as early as the first or as late as the fifth decade occurs first in the coronary sinuses Profound aortic regurgitation may precede evidence of dilatation of the aorta on ordinary radiographic study The clinical features of acute dissection are discussed on p 1338

Less common cardiovascular complications are bacterial endocarditis superimposed on minor

FIG 199 Composite chart relating manifestations of the Marfan syndrome to a single defect (*pedigree of causes*)

changes of the heart valves interatrial septal defect, and incomplete coarctation

Other internal ramifications include cystic disease of the lung and recurrent spontaneous pneumothorax

Differential Diagnosis Given cardiovascular and skeletal manifestations consistent with the Marfan syndrome one cannot be certain of the diagnosis unless ectopia lentis the most specific of the components of the syndrome can be demonstrated or unless close relatives display unmistakable evidence of the disease Confusion results from the fact that there is wide variability in the clinical severity of this syndrome and its individual components display some independence in their severity ("expressivity") or even in whether they are present at all (penetrance) When the mutant gene for this syndrome occurs in pyknic stock the affected person is likely to display less impressive skeletal abnormalities The patient must be judged against the background of his family

Intrauterine insults to the embryo such as maternal rubella can produce changes in the eye heart and skeleton (including arachnodactyly) which superficially suggest the Marfan syndrome

Inheritance The Marfan syndrome is usually inherited as an autosomal dominant

Pathology and Basic Defect The main histologic abnormality is that of the aortic media Probably normal at birth it undergoes changes which in the mildest form are identical with Erdheim s cystic medial necrosis seen in other settings In its advanced form there are loss of elastic fibers scarring hyperplasia of smooth muscle in large whorls and dilatation of the vasa vasorum What element of connective tissue is fundamentally defective is unknown The elastic fiber is under suspicion

THE EHLERS DANLOS SYNDROME

Definition The Ehlers Danlos syndrome (synonyms cutis hyperelastica India rubber men dermatorrhexis with dermatochalasis and arthrochalasis etc) is a heritable and generalized disorder of one element of connective tissue clinically manifested by fragility and hyperelasticity of the skin and loose jointedness

Clinical Manifestations Characteristically the skin can be stretched through an unusually great range yet returns promptly to its normal position on release (Fig 200) Later on the skin may lose its elasticity become truly *cutis laxa* and hang in flabby folds or wrinkles The skin is fragile so that minor trauma is likely to produce gaping fish mouth wounds which bleed little and hold sutures poorly There is easy bruisability Firm spherules up to about 1 cm in diameter develop subcutaneously can be moved about through a considerable range and can be demonstrated radiographically because of calcification Cigarette paper" scars develop over the knees shins etc So called molluscoid pseudotumors develop on the knees ankles and elbows as soft poorly outlined swellings that can be several centimeters in diameter

The loose jointedness results in genu recurvatum habitual dislocation of various joints flat feet etc Recurrent hydrarthrosis may result from the repeated trauma due to poor stabilization especially in the knees

Internal ramifications include diaphragmatic hernia or eventration of the diaphragm ectasia of portions of the gastrointestinal and respiratory tracts and spontaneous pneumothorax

Inheritance The Ehlers Danlos syndrome is usually inherited as an autosomal dominant

Pathology and Basic Defect The basic defect appears to be abnormality in the way the collagen "wickerwork is arranged such that excessive extensibility of collagenous structures is possible The normal elastic tissues appear to function in restoring structures to their normal position the elastic fibers may in fact be hyperplastic possibly in response to the repeated stimulus of extra stretching

OSTEOGENESIS IMPERFECTA

Definition Osteogenesis imperfecta (synonyms fragilitas ossium osteopsathyrosis idiopathica disease of Eddowes Lobstein van der Hoeve Vrolik etc) is a heritable generalized disorder of one element of connective tissue with clinical manifestations in the eye (blue sclerae) the ear (progressive deafness) the skeleton (especially multiple fractures see p 671) the joints (loose jointedness) and the skin The nosography of this syndrome has been much confused because of this wide variability in its clinical expression Osteogenesis imperfecta *congenita* and *tarda* have been separated A further separation of the tarda type into *levis* and *gravis* forms has been suggested A hereditary disease characterized by fragility of bones without blue sclerae has been claimed as a separate entity and called specifically *osteopsathyrosis idiopathica* Until there is convincing evidence to the contrary however the information available leads the writer to maintain that *all the several clinical pictures which have been described and which go by separate names in many instances are one and the same disease which has wide systemic ramifications and an exceedingly great range of clinical severity*

Clinical Manifestations *Skeleton* Multiple fractures with trivial trauma are a main feature (Fig 201) Intrauterine fractures may permit antenatal diagnosis Usually after puberty the victim of this disease becomes less subject to fractures susceptibility may return in later life especially after the

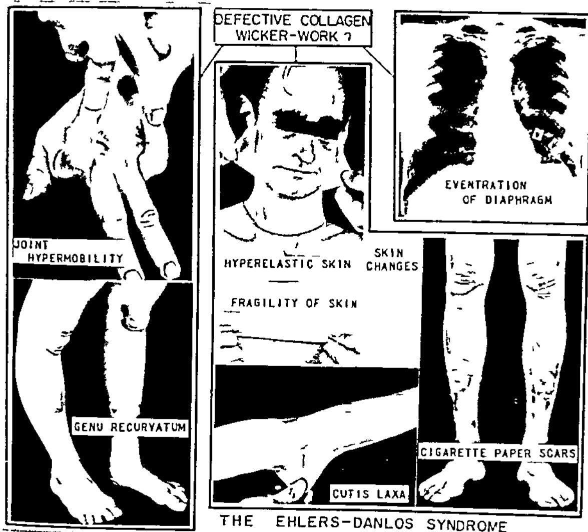


FIG 200 Pedigree of causes for the Ehlers Danlos syndrome

menopause in the female Bowing of bones porotic appearance by x ray without fracture "codfish" or "hourglass" vertebrae platybasia (basilar impression of the skull p 1543) are all features Dwarfism with short legs and relatively large head may be confused with achondroplasia The French artist Toulouse Lautrec is thought to have had osteogenesis imperfecta The calvarium tends to bulge laterally and the head and face have a triangular configuration which often permits diagnosis from photographs alone

Eye The change in the sclera which may be various shades of blue is the only important ocular feature

Ear The deafness has the clinical features of conventional otosclerosis variable age of onset steady progression, and likelihood to begin during pregnancy The tympanic membrane may be blue like the sclera

Joints Loose jointedness is one of the four cardinal features of the disease It is responsible at least in part, for flat feet kyphoscoliosis and habitual dislocation of joints Weakness of ligaments and tendons responsible for the loose-jointedness sometimes results in rupture of tendons from relatively minor stress

Others. Hernia is frequent The teeth are characteristically small misshapen and bluish yellow Kyphoscoliosis can lead in later life to cardiorespiratory complications

Inheritance Usually osteogenesis imperfecta is clearly inherited as an autosomal dominant. Some aspects of its genetics are still confused Certain features especially those concerning sporadic cases suggest a recessive mode of inheritance

Pathology and Basic Defect In the bones peculiar basophilic-staining material is found in place of osteoid In other tissues there is a sparsity of

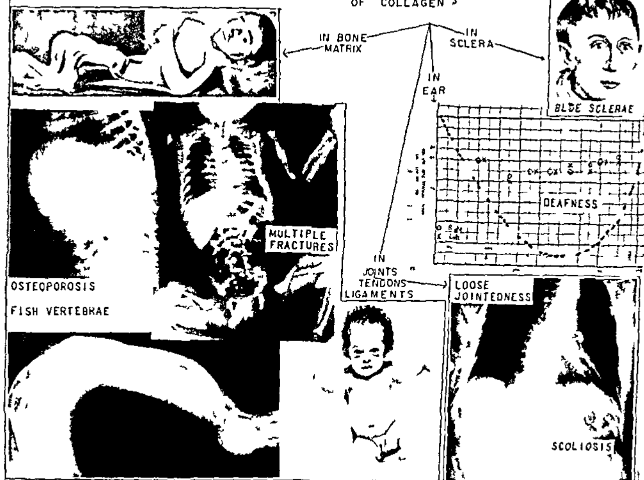


Fig 201 Pedigree of causes for osteogenesis imperfecta

collagen fibers and replacement by fibers with tinctorial and other characteristics of reticulin There appears to be a generalized defect in maturation of collagen

PSEUDOXANTHOMA ELASTICUM

Definition Pseudoxanthoma elasticum (synonyms PXE Groenblad Strandberg syndrome) is a hereditary generalized disorder of one element of connective tissue resulting in premature breakdown of the skin in exposed areas angioid streaks in the fundus oculi and hemorrhage from arterial degeneration

Clinical Manifestations *Skin* In the second third or fourth decade of life patients affected by PXE are likely to develop changes in the skin of the neck axillae inguinal areas and periumbilical zone consisting of thickening grooving and formation of yellowish diamond shaped rectangular and polygonal nodules (Fig 202) The skin in involved areas becomes inelastic lax and redundant In females the changes in the neck may be cosmetically disturbing

Eye Angioid streaks develop at a variable time often as early as the second decade They are brownish or gray and four or five times wider than the veins but resemble vessels in the manner in which they course over the fundus Proliferative changes occur in the retina with angioid streaks as points of origin Hemorrhage contributes further to the ocular damage which may progress to near blindness

Arterial Tree Weak or absent pulses may be found in the extremities Calcification of arteries is often demonstrable by radiography early in life Intermittent claudication and easy fatigability of the arms and legs occur Many of the affected persons suffer from angina pectoris and hypertension Recurrent gastrointestinal hemorrhage is the problem which most often brings the patient to the attention of the internist Occasionally some lesion such as peptic ulcer or hiatus hernia is discovered and the vascular disease of PXE is considered only

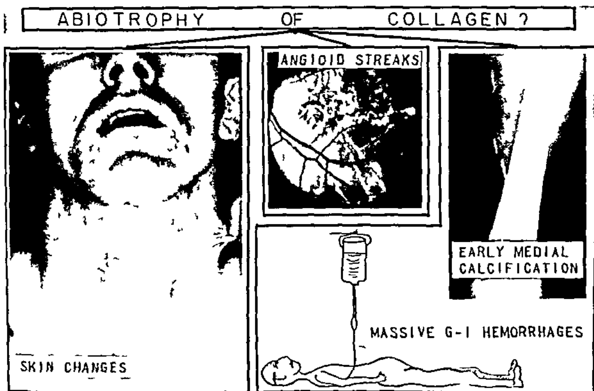


Fig 202 Pedigree of causes for pseudoxanthoma elasticum

an aggravating factor More often no such lesion *is found Hemorrhage from other sites—uterine* urinary nasal or subarachnoid—may occur

Inheritance Pseudoxanthoma elasticum behaves genetically like an autosomal recessive

Pathology and Basic Defect The skin and media of arteries of intermediate and smaller size (and occasionally the endocardium and pericardium) become the site of markedly altered connective tissue fibers which are basophilic have an affinity for calcium and display the tinctorial characteristics of elastic fibers In some areas material of this description is reduced to amorphous or granular accumulations The basis for angioid streaks appears to be basophilic change and subsequent crazing (cracking) of Bruck s membrane behind the retina A growing body of evidence suggests that fundamentally PXE is a hereditary weakness of collagen fibers (not elastic fibers) which renders them prone to undergo what some call elastotic degeneration under stress

THE HURLER SYNDROME

Definition The Hurler syndrome (synonyms gargoylism Hunter Hurler Pfaundler syndrome lipochondrodystrophy dysostosis multiplex, etc) is thought to be a generalized heritable disorder of one element of connective tissue manifested by a characteristic malformation of the skeleton stiff *joints deafness lesions of the* arterial retina and heart valves hepatosplenomegaly corneal clouding and impairment of intellect (Fig 203)

Clinical Manifestations Although previously considered the exclusive property of the pediatrician this syndrome is coming more to the attention of the internist Milder forms of the disease are consistent with survival to adulthood and improved supportive measures permit longer survival of more severely affected cases The child is often considered normal at birth with time the abnormality in pattern of growth of the skeleton becomes evident and slowing of intellectual development, deafness enlargement of the liver and spleen and clouding of the cornea set in The deformity of the facial bones results in stertorous respiration frequent upper respiratory infection and mouth breathing which creates an appearance superficially suggesting cretinism Virtually all joints of the body display reduced mobility Dyspnea precordial pain and congestive heart failure develop Murmurs referable to any of the four valves of the heart can develop The mitral and aortic valves are most often affected Sudden death seemingly cardiac in origin is frequent Intercurrent respiratory infection is also a common cause of death

Inheritance There are probably two genetic variants of this disease—one inherited as an autosomal

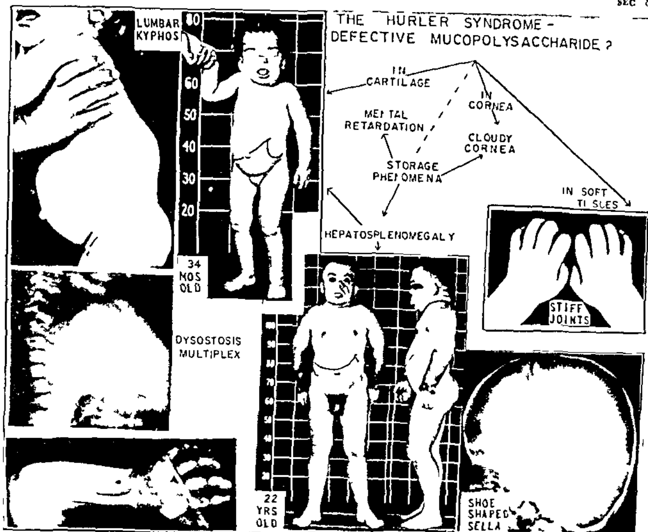


Fig 203 Pedigree of causes for the Hurler syndrome

recessive and one as a sex linked recessive like hemophilia In the variety with sex linked inheritance the cornea is less likely to be affected intellect is less severely impaired gibbus (or lumbar kyphosis) is less frequent and survival to a later age even the forties is possible Otherwise the clinical features of the two varieties are identical

Pathology and Basic Defect Cartilage fascia tendons periosteum blood vessels heart valves meninges and cornea show characteristic cells which are thought to arise from fibroblasts these are distended by a substance with properties of a polysaccharide and have been designated as gargoyle cells Material presumably identical with that in the fibroblasts balloons the nerve cells of the central nervous system peripheral ganglions and retina the Kupffer and parenchymal cells of the liver the reticulum cells of spleen and lymph nodes and the epithelial cells of endocrine glands Extensive deposits may be found in the intima of coronary arteries aorta and pulmonary artery The heart valves become scarred and deformed The polysaccharide nature of the intracellular deposits has been confirmed in all tissues except the brain where some consider the material to be phospholipid

The basic defect is thought to concern either mucopolysaccharide or *structural polysaccharide* the latter term referring to a component of cellular structure

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262 COLLAGEN DISORDERS

B V Jager

The term *diffuse collagen disorders* is applied to a group of diseases in which extensive involvement of connective tissue appears to be the salient fea

ture Rheumatoid arthritis rheumatic fever poly arteritis nodosa systemic lupus erythematosus diffuse scleroderma (progressive systemic sclerosis) and dermatomyositis usually are placed in this category Both clinical and pathologic considerations make it appropriate to include serum sickness here In addition many observers include other disorders such as allergic purpuras (p 1203) certain cases of Loeffler's syndrome (p 1397) thromboangiitis obliterans (p 1341) and subacute bacterial endocarditis (p 970)

Certain of the diseases enumerated above are considered elsewhere in this book This and the following chapter concern *serum sickness polyarteritis nodosa systemic lupus erythematosus diffuse scleroderma dermatomyositis* and *polymyositis* Also mention is given to *scleredema adultorum* because of its clinical similarity to scleroderma *Cranial arteritis* and *Wegener's granulomatosis* both unusual are considered briefly The main characteristics of *Weber Christian disease* also are presented although it is recognized that this disease differs significantly from the others

Pathologically the four diseases polyarteritis nodosa systemic lupus erythematosus diffuse scleroderma and dermatomyositis have many features in common In each there may be proliferative and degenerative changes in connective tissue Most familiar is the so-called fibrinoid" degeneration in which collagenous connective tissue assumes the tinctorial characteristics of fibrin It is not known what gives rise to this fibrinoid substance Arteritis or vasculitis may be found in all of these diseases thus is least frequent in dermatomyositis

Clinically also there are many similarities Raynaud's phenomenon may occur in any one of them Retina lesions are observed in certain cases with each disease Except in dermatomyositis arthralgia and arthritis are frequent Erythematous and purpuric skin lesions may be observed in any of the four Visceral lesions especially in the heart lungs and kidney are encountered in these disorders again being least common in dermatomyositis Systemic lupus erythematosus stands clearly apart from the others in this condition alone is there a plasma or serum factor capable of producing the so-called L E cell

The etiology of none of these diseases is known It is tempting to assume that they all represent a particular type of allergic response This is all the more alluring since serum sickness disease induced in rabbits reproduces many of the pathologic characteristics of polyarteritis nodosa rheumatic fever and glomerulonephritis However definitive proof that allergy is responsible for these four clinical entities is lacking

A comparison of the symptomatology of the four diseases is shown in Table 133 p 1700 The tabulation of frequency of symptoms is arbitrary and is intended as a guide to the likelihood of a given symptom in the well-developed stage of the disease but not necessarily in the initial or terminal phase

SERUM SICKNESS

Serum sickness is a delayed systemic reaction resulting from administration of foreign serum or certain drugs to susceptible individuals The usual clinical manifestations include fever skin eruptions arthralgia edema and lymphadenopathy

Serum sickness was recognized when large amounts of whole horse serum were introduced into man for the prophylaxis and treatment of diphtheria Not only whole horse serum but also refined globulin fractions containing antitoxin to diphtheria and tetanus toxins may give rise to serum sickness as does bovine albumin which was tested in man as a plasma substitute In addition sensitivity to a number of drugs including sulfonamides penicillin and iodides may produce the same symptom complex

The production of serum sickness in experimental animals has evoked considerable interest. After a single large parenteral injection of whole horse serum bovine albumin or bovine globulin relatively few symptoms are noted in the rabbit When animals are sacrificed at intervals after the administration of serum however histologic examination often shows lesions similar to those of polyarteritis nodosa rheumatic fever and glomerulonephritis in man The acute lesions occur at the time when the administered antigen (heterologous serum) is being rapidly removed from the plasma. Usually healing of lesions is in progress by the time that antibody to the injected protein is demonstrable in the serum Administration of ACTH or cortisone to the rabbit following injection of the foreign serum protein reduces the incidence of lesions

Serum sickness in man usually is a brief disease with an abrupt onset 3 to 21 days after administration of a serum product or a drug Most reactions begin from the fourth to the tenth day Early in the illness there is fever with arthralgia and myalgia of variable severity Occasionally there is swelling of the joints An urticarial eruption occurs as does a feeling of soreness of the throat. The lymph nodes become enlarged and the spleen may become palpable Later erythematous and sometimes purpuric skin rashes are to be seen Cardiac arrhythmias are encountered and rarely there is pericarditis There may be diarrhea which sometimes is hemorrhagic Anuria or oliguria may appear but seldom persists longer than a few days A variety of neurologic disturbances have been noted in serum sick

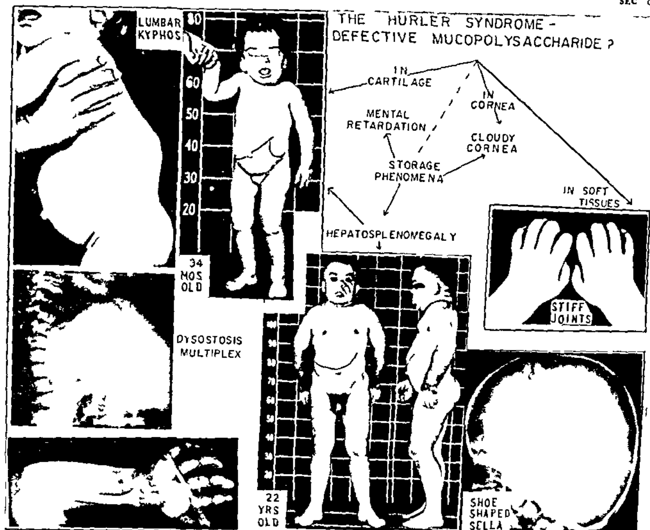


Fig 203 Pedigree of causes for the Hurler syndrome

recessive and one as a sex linked recessive like hemophilia In the variety with sex linked inheritance the cornea is less likely to be affected intellect is less severely impaired gibbus (or lumbar kyphosis) is less frequent and survival to a later age even the forties is possible Otherwise the clinical features of the two varieties are identical

Pathology and Basic Defect Cartilage fascia tendons periosteum blood vessels heart valves meninges and cornea show characteristic cells which are thought to arise from fibroblasts these are distended by a substance with properties of a polysaccharide and have been designated as gargoyle cells Material presumably identical with that in the fibroblasts "balloons the nerve cells of the central nervous system peripheral ganglions and retina the Kupffer and parenchymal cells of the liver the reticulum cells of spleen and lymph nodes and the epithelial cells of endocrine glands Extensive deposits may be found in the intima of coronary arteries aorta and pulmonary artery The heart valves become scarred and deformed The polysaccharide nature of the intracellular deposits has been confirmed in all tissues except the brain where some consider the material to be phospholipid

The basic defect is thought to concern either mucopolysaccharide or *structural polysaccharide* the latter term referring to a component of cellular structure

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262 COLLAGEN DISORDERS

B V Jager

The term *diffuse collagen disorders* is applied to a group of diseases in which extensive involvement of connective tissue appears to be the salient fea

tively small number of cases obvious hypersensitivity to serum or to a drug initiates the process In others symptoms appear during convalescence from an infection much as acute rheumatic fever follows streptococcal pharyngitis In most cases however no predisposing factor is apparent Bronchial asthma cutaneous eruptions severe abdominal pain cardiac failure glomerulonephritis arthralgia or arthritis myalgia and peripheral neuritis are only a few of the presenting symptoms or findings which may be observed

As the disease progresses almost any region of the body may be affected Frequently it is the multiplicity of superficial and visceral lesions which first suggests the diagnosis A variety of cutaneous eruptions may be observed Purpura erythema nodosum erythema multiforme and focal necroses suggesting embolic manifestations may be encountered There may be subcutaneous nodules Many patients present themselves primarily for neurologic disorders Subjective paresthesias sensory impairment muscle tenderness and muscle wasting suggest the presence of peripheral neuritis Headaches convulsions papilledema and cranial nerve palsies may be confused with cranial neoplasms Muscle tenderness may appear even in the absence of peripheral neuritis Painful joints which may or may not be swollen and tender are observed often In some instances deformities of joints that resemble changes in rheumatoid arthritis are found Retinal hemorrhages and exudates are frequent

The cardiovascular system frequently is implicated At least half the patients develop hypertension during the illness Pericardial friction rubs cardiac enlargement and tachycardia out of proportion to existent fever or anemia may call attention to heart injury Systolic murmurs are noted frequently but diastolic murmurs are unusual unless there has been previous acute rheumatism Electrocardiographic abnormalities are not unusual A few patients develop cold hypersensitivity of the Raynaud type

A number of patients develop asthma and less frequently cough hemoptysis pulmonary infiltrations or pleurisy

Involvement of the gastrointestinal tract may be signalized by nausea vomiting diarrhea or melena Perforation of the intestine or gallbladder has been observed The character of the abdominal pain may suggest a surgical emergency such as infarction of bowel acute appendicitis or acute cholecystitis Indeed these conditions may be present at operation and only after histologic examination is it possible to recognize the disease as polyarteritis nodosa Polyarteritis is a common cause of true infarction of the liver

Renal injury is observed in a relatively large proportion of cases There may be gross hematuria more often other symptoms and signs of impaired renal function are observed and they can progress to uremia Hypertension usually is present when renal damage is marked

During the course of the disease intermittent fever is usual The height and type of the fever vary Loss of weight and of strength often are striking

Death results most often from renal injury with concomitant hypertension or from heart failure secondary to extensive myocardial damage A variety of other visceral lesions may lead to death however

Laboratory Data Moderate normocytic anemia is a common finding Characteristically the leukocyte count is elevated ranging from 12 000 to 50 000 per cubic millimeter Very occasionally there is leukopenia The differential count usually discloses an increase in polymorphonuclear leukocytes In about one fifth of the cases a marked eosinophilia is observed in a random examination When repeated differential counts are made eosinophilia often transient is found in a greater proportion of cases The urine may contain albumin casts erythrocytes and white blood cells Spinal fluid is usually normal even when there is peripheral neuritis In the serum slight hypoalbuminemia and moderate hyperglobulinemia are common findings

Diagnosis It usually is not possible to establish a diagnosis of polyarteritis nodosa in the absence of histologic evidence of arteritis Clinically the changing clinical picture with evidence of involvement of many tissues or organs and the remittent course are suggestive as are leukocytosis eosinophilia and urinary abnormalities The correct diagnosis is established in approximately one third of cases during life

When the disease is suspected biopsies should be made of skin subcutaneous tissue and muscle If the biopsy and the clinical picture are compatible the diagnosis of polyarteritis nodosa is justified Caution should be exercised in the acceptance of this diagnosis on a report of histologic changes alone The cutaneous lesions of erythema multiforme erythema nodosum Weber Christian disease and nodular vasculitis may show similar vascular abnormalities In addition one finds that similar lesions occur in rheumatoid arthritis and systemic lupus erythematosus and less frequently in diffuse scleroderma and dermatomyositis Moreover patients with drug sensitivity and with serum sickness may show the lesions of polyarteritis nodosa It is debatable whether or not such patients should be given a diagnosis of this disease These drug and serum sensitivity vascular lesions often seem to be transient and full clinical recovery is frequent By

ness Most common is a unilateral radiculitis or neuritis affecting particularly muscles in the shoulder girdle Infrequently there is a polyneuritis or a meningoencephalitis

Laboratory findings are relatively few There often is a moderate leukocytosis The differential count early in the disease may reveal considerable numbers of plasma cells There is no eosinophilia with the illness produced by foreign serums although it may be found with the illness induced by drugs As in rabbits antibodies to the foreign serum appear late in the disease The urine may contain protein leukocytes erythrocytes and casts Electrocardiograms may reveal conduction defects or arrhythmias

Serum sickness rarely lasts more than several weeks Epinephrine injections or antihistaminics produce prompt disappearance of urticaria Acetyl salicylic acid or sodium salicylate usually is helpful in controlling the discomfort of arthralgia and myalgia For severe symptoms short courses of ACTH or cortisone and related steroids are effective

Serum sickness usually is benign and full recovery is to be expected A few patients have died from serum sickness from the drug induced sickness which resembles it or from the disease for which the agent was given Upon histologic examination the tissues of these individuals have sometimes shown an arteritis indistinguishable from that observed in polyarteritis nodosa

POLYARTERITIS NODOSA

Definition This is a systemic disease chronic or subacute in its course and frequently fatal characterized by damage to arterioles and medium sized arteries The distribution of the vascular lesions varies with resulting diversity of visceral involvement and a broad spectrum of clinical manifestations

Synonyms or allied afflictions include periarteritis nodosa disseminated necrotizing vasculitis generalized arteritis and necrotizing angiitis

Etiology In experimental animals histologic lesions of necrotizing arteritis similar to those seen in human cases of polyarteritis can be produced by such diverse means as sensitization to foreign proteins induction of hypertension or administration of desoxycorticosterone acetate In some patients with polyarteritis nodosa sensitization to heterologous serum or to drugs such as sulfonamides iodides and penicillin clearly seems to have produced the disease In the majority of cases however there is no obvious evidence of sensitization Efforts have been made to separate the clinical cases of polyarteritis into various groups For example the *hypersensitivity* type is said to have a short course the lesions all appear of the same age histologically and the pulmonary vessels are frequently affected In a second type the course is prolonged and intermittent and pulmonary vessels are spared A third type has been observed to occur terminally in patients who have had marked hypertension either essential or secondary to renal disease Such separation suggests a varied etiology for the human disease polyarteritis nodosa However, it is not usually possible to classify the disease in a given patient on clinical grounds or by post mortem studies

Incidence The ages of affected individuals have ranged from three months to seventy eight years but the highest incidence is between forty and sixty years of age The ratio of affected males to females is variously stated as 3 1 or 4 1

Pathology This disease primarily affects medium sized and small arteries and arterioles Large arteries may be involved through lesions of the vasa vasorum Rarely veins are affected Gross anatomic findings are variable Small aneurysms may be noted in mesenteric arteries or in arteries elsewhere More often one detects only visceral lesions resulting from ischemia or hemorrhage Lymph node enlargement splenomegaly and serous effusions occur occasionally

Histologically the characteristic changes are found in small and medium sized arteries and in arterioles Often only short segments of a vessel are affected The entire circumference of the vessel or only a portion of it may be involved The distribution of vascular alterations from case to case varies considerably In approximately decreasing frequency lesions of vessels are observed in the kidney heart liver gastrointestinal tract mesenteric vessels spleen pancreas lung muscles and peripheral nerves Almost any organ and tissue of the body may be affected

The fundamental abnormality consists of necrosis and fibrinoid change of the vessel wall with accompanying leukocytic infiltration Thrombosis of the injured vessel may result or an aneurysm may develop With healing fibrosis appears and may lead to narrowing or obliteration of the lumen In autopsy studies it is often possible to demonstrate vessels in all stages of degeneration and repair This is in keeping with the remittent clinical pattern so frequently observed

Clinical Manifestations The symptomatology of this disorder is as diversified as that of syphilis but unfortunately it is not detectable by any serologic test Only by histologic examination of material obtained by biopsy or necropsy can a positive diagnosis be made

The onset may be insidious or abrupt In a rela

ened glomerular tuft basement membrane ("wire loop lesion) periarterial fibrosis in the spleen (onionskin lesion) focal necrosis of lymph nodes and hematoxylin bodies (amorphous globules of desoxyribonucleic acid) situated in various tissues such as the heart kidney or lymph nodes

Clinical Manifestations Like the pathologic changes the clinical manifestations of this disorder are extremely varied This has become more evident since the development of the L E cell test which is regarded as specific for systemic lupus erythematosus The presenting clinical picture may be *hemolytic anemia* or *thrombocytopenic purpura* Frequent early symptoms are fever arthralgia and arthritis pleuritic pain loss of weight dyspnea and orthopnea The skin eruption formerly regarded as almost essential for the diagnosis can precede systemic symptoms for years It may appear early or late in the illness and may be transient As the disease progresses constitutional symptoms such as fever tachycardia anorexia and loss of weight become severe Remission of all symptoms may ensue and persist for long periods Frequently with exacerbations symptoms become increasingly severe and additional organs tend to become affected Usually the outcome is fatal however the course of this disease extends over 5 to 15 years in many instances

The characteristic skin lesion is an erythematous eruption over the malar region and the bridge of the nose—the butterfly distribution The lesions are raised and indurated Long standing lesions tend to have sharp margins and may show silvery scales which when scraped away reveal dilated follicles When the typical rash of lupus erythematosus is present and when there are no apparent constitutional symptoms the term *discoid lupus erythematosus is applied Although it has been thought that* it is rare for discoid lupus to become a systemic disorder careful studies of patients with discoid lupus erythematosus indicate that previously unsuspected clinical and laboratory abnormalities are often present

The Senear Usher syndrome is regarded as a variant of systemic lupus erythematosus In this disorder erythematous scaly lesions of the face and neck are found in conjunction with bullous lesions over the rest of the body The eruptions apart from those on the face simulate pemphigus vulgaris

In addition many other skin changes may be encountered including telangiectasia pigmentation (focal or diffuse) purpura ecchymoses indurated nodules in the finger tips urticaria erythema multiforme or nodosum and patchy or total alopecia Infrequently papular and ulcerated lesions are observed in the mouth

Nearly all patients develop joint symptoms There may be only a migratory arthralgia Frequently there are tenderness and swelling of several joints A number of patients show deformities of joints which cannot be distinguished from rheumatoid arthritis

Edema is another common finding This may be periorbital dependent diffuse or focal in character

Pleuritic pain frequently develops and may be associated with a friction rub or an effusion Pericardial rubs and effusions also may be observed In some patients roentgenograms of the chest disclose patchy atelectasis of the lower lobes of the lungs with an elevated diaphragm In addition there may be chronic pulmonary infiltrations of varying extent Patients with systemic lupus erythematosus appear to be predisposed to bacterial pulmonary infections It may be difficult or impossible to differentiate primary lupus pneumonias from those due to infectious agents

The cardiovascular system shares in the stigmas of systemic lupus erythematosus Apart from pericardial changes there may be myocardial damage with resultant dilatation of the heart and cardiac insufficiency Systolic murmurs are frequent Hypertension of significant degree occurs in less than 20 per cent of cases Even patients with markedly impaired renal function often are normotensive This feature may be useful in differentiating this disorder from other types of chronic renal disease where hypertension is to be expected A few patients give a history of hypersensitivity of the fingers to cold usually of the Raynaud type This type of vasomotor disturbance may appear long before other manifestations

There is no pathognomonic retinal lesion in this disorder Hemorrhages exudates or cytoid bodies are found in about one fourth of patients who are *observed for long periods Abdominal pain is intense* and prolonged in some patients There may be diarrhea and occasionally melena The liver often is moderately enlarged Jaundice is rare except in the few individuals who have a hemolytic anemia Splenomegaly is noted in about one fifth of the cases

In two thirds of the cases studied for long periods the urine contains protein and granular casts Frequently the urine becomes normal during remissions A few patients have massive proteinuria which may be associated with the other findings of the nephrotic syndrome Approximately 10 per cent of all cases progress to renal insufficiency

Regional or diffuse lymph node enlargement is present in approximately one third of the patients The cervical chain of nodes is particularly prone to enlargement in this disease

There is growing evidence that the central nervous system is implicated frequently Transient cerebrospinal pleocytosis with headache and stiff

Table 133 COMPARISON OF THE CLINICAL CHARACTERISTICS OF POLYARTERITIS NODOSA, SYSTEMIC LUPUS ERYTHEMATOSUS, SCLERODERMA, AND DERMATOMYOSITIS*

Clinical characteristics	Polyarteritis *nodosa*	Systemic lupus *erythematosus*	Diffuse *scleroderma*	Dermatomyositis
Sex incidence M F	4 1	1 4	2 1	1 1
Commonly noted age of onset (in years)	20–40	15–40	30 50	10–50
Arthralgia or arthritis (relative frequency)	+	++	++	±
Cutaneous lesions	++	+++	+++	+++
Cardiac involvement	++	++	+	+
Hypertension	++	+	±	−
Pulmonary lesions	+	+	+	−
Pleuritis with or without effusion	±	++	−	−
Abdominal pain	+++	+	±	−
Impaired renal function	++	+	±	−
Lymph node enlargement	+	++	+	+
Splenomegaly	±	++	±	±
Peripheral neuritis	+	±	±	±
Focal brain lesions	+	+	−	−
Muscle inflammation	+	+	+	+++
Abnormal laboratory findings				
Anemia	++	+++	±	±
Leukocyte count (usual)	Elevated	Reduced	Normal	Normal
Eosinophilia	+	±	±	+
Abnormal urinary sediment	++	+++	+	±
L E cells	−	+++	−	−

* Frequency roughly estimated as follows +++ = 60–100% ++ = 40 59% + = 20–39% ± = less than 20% − = no greater than in the ordinary population of the same age

contrast the vascular lesions in the many cases of polyarteritis are recurrent and chronic progressive illness is the sequence

Therapy Spontaneous remissions are encountered frequently in this disease In severely ill patients without serious renal damage the use of ACTH or cortisone and related steroids may produce good relief of symptoms but these drugs can aggravate *renal insufficiency in individuals* with already damaged kidneys

SYSTEMIC LUPUS ERYTHEMATOSUS

Definition *Systemic lupus erythematosus usually* is a chronic disorder in which there are remissions and exacerbations The clinical findings are variable In a typical instance there may be intermittent fever arthralgia or arthritis a characteristic skin eruption proteinuria leukopenia hyperglobulinemia and a positive test for L E cells Certain variants of this disorder have been termed *Libman Sacks disease* (atypical verrucose endocarditis) and the *Senear Usher syndrome*

Incidence About 80 to 85 per cent of reported cases have occurred in females The disease may appear at any age but is most commonly seen between the ages of fifteen and forty years

Etiology The cause is not known Frequently the earliest symptoms follow intense exposure to sunlight In other instances infections and trauma of various sorts appear to initiate the process A few patients who have received 1 hydrazinophthalazine (hydralazine Apresoline) for control of hypertension *develop an illness resembling acute rheumatoid* arthritis When the medication is continued some of these individuals show skin eruptions polyserositis fever anemia proteinuria and positive tests for L E cells It is not claimed that this syndrome is identical with the disease systemic lupus erythematosus Nonetheless the similarity of the two conditions is striking

Pathology In autopsied cases gross findings *often are slight and may be absent The serous* membranes (pleura pericardium peritoneum joints) may exhibit thickening with or without effusions Moderate splenomegaly and focal or dif*fuse lymph node enlargement occur* Small and large verrucose nonbacterial endocardial lesions involving the heart valves and adjacent mural endocardium are found in approximately 30 per cent of cases Frequently the anatomic changes are complicated by terminal bacterial infections

Histologically connective tissues show fibrinoid changes and leukocytic infiltrates Hemorrhage may be observed about capillaries arterioles may be thickened and narrow*ed or contain thrombi It is* said that typical skin lesions present a characteristic microscopic appearance Other features are thick

gradually withdrawn until another acute episode occurs In some individuals it is necessary to maintain constant treatment with ACTH or with cortisonelike drugs A gel of ACTH may be given once daily as an intramuscular injection It is estimated that a dosage of 100 mg daily of this substance will provide maximal adrenal stimulation After a satisfactory clinical response is achieved the dosage may be gradually decreased so long as it suffices to prevent serious symptoms Initially cortisone acetate usually is administered orally at 8 hr intervals in a total of 200 to 300 mg per 24 hr Potassium chloride (8 to 12 Gm daily) and a low salt diet should be prescribed Often it is possible to reduce the daily dosage of cortisone to a maintenance level of 50 to 100 mg Instead of cortisone acetate one may use an oral preparation of hydrocortisone Here the dosage is approximately 80 per cent the amount of cortisone Prednisone and prednisolone although more expensive than cortisone are effective in a dosage of 20 to 25 mg per day given in three doses It may be necessary to use five to ten times these doses of steroids initially to achieve a response In particular the acute hemolytic anemia seen in this disorder seems unresponsive until large quantities of cortisone or related drugs are given

For less severe symptoms aspirin often will keep the patient comfortable

It is also possible to use quinacrine (Atabrine) This drug is useful in simple discoid lupus erythematosus and may be helpful in those with the systemic form of the disease It is recommended that the initial dose be 100 mg three times a day after meals If no response occurs and if no toxicity supervenes the dose can be increased to a maximal daily dose of 600 mg

General supportive measures are indicated Patients should avoid exposure to sunlight

SCLERODERMA

Definition Scleroderma is a disease characterized pathologically by an alteration in collagen tissue and clinically by focal or diffuse induration of the skin Fibrosis in visceral structures is frequent There may or may not be associated vasomotor disturbances and endocrine disorders The term *progressive systemic sclerosis* has been suggested for the disease but has not achieved wide usage

The etiology is unknown Endocrine vasomotor or neurotrophic factors and hypersensitivity have been suggested Diffuse scleroderma is a relatively uncommon disease which usually occurs between the ages of thirty and fifty years It is slightly more frequent in women

Pathology In the skin there is atrophy of the epidermis flattening of the dermal papillae atrophy of the dermal appendages and fragmentation of elastic tissue in the corium The corium appears more dense than usual because of swelling proliferation and fusion of collagen fibers which occasionally show fibrinoid degeneration Small arteries in the corium are thickened and narrowed Early there may be edema and a moderate mononuclear cell infiltration Increases in collagen tissue may be present in muscle fascia in muscle itself and in various viscera especially the heart and lungs In the esophagus stomach and intestine there are atrophy of smooth muscle and fibrosis of the submucosa Ulceration of the lower esophagus is not unusual Occasionally the kidneys show a peculiar lesion in which marked intimal thickening occurs in interlobular arteries leading to ischemic necrosis of the renal cortex

The disease exists in a focal form in which are found indurated cutaneous lesions which tend to follow the distribution of peripheral nerves This disorder known as *morphea* or *scleroderma circumscripta* is rarely associated with the more diffuse form of the disease and rarely presages its development Diffuse scleroderma varies in site of onset and in extent Not infrequently the earliest and most extensive skin changes are to be found on the hands forearms and face In other patients the neck trunk and proximal portions of the arms may be principally affected

Clinical Manifestations The onset often is insidious Early symptoms include slight fever edema which may be diffuse or focal arthralgia and mild arthritis Many patients give a history of vasomotor disturbances particularly of the Raynaud type for months or years preceding the changes in the skin

As the disease progresses conspicuous changes are found in the skin especially of the face neck and upper extremities The severity of the process in different parts of the body may vary greatly The involved skin has a waxy sheen is taut feels thickened and cannot be lifted from the underlying structures In the affected areas pigmentation depigmentation loss of hair or telangiectasia are often noted Occasionally there may be cyanosis and erythema When the face is involved the features assume a masklike appearance and there may be limitation of the movements of the jaw Induration of the skin of the extremities and girdle regions may give rise to limited motion and contractures Clubbing and other deformities of the fingernails may be observed Trophic ulcerations may develop in any involved area especially on the finger tips Paresthesias and reduction in sensory perception may be present Indurated lesions may be found on the tongue and gums

The muscles may display induration and atrophy In some instances they are also tender usually the result of an associated polymyositis In a few pa

neck occurs during the course of the disease in many patients Epileptiform seizures may appear early or late in the illness The psychoses and confusion noted in some patients are thought to be ascribable to an organic brain syndrome resulting from multiple small infarcts of the cerebral hemispheres Particularly in the late stages of the disease one encounters neurologic damage evidenced by gross tremors or hemiplegia Electroencephalograms often are abnormal in systemic lupus erythematosus Polyneuritis is present in less than 2 per cent of the cases

Laboratory Data Examination of the blood usually reveals a normochromic anemia Occasionally there is an acute hemolytic anemia Cold agglutinins positive direct Coombs tests and less frequently positive indirect Coombs tests are encountered *with or without hemolytic anemia* The leukocyte count is low (2 000 to 4 000 per cubic millimeter) but may be normal or elevated Differential counts in some instances reveal a relative lymphopenia with a preponderance of neutrophils An increase in the number of eosinophils is rare There may be extreme thrombocytopenia In some patients a circulating anticoagulant has been found often in conjunction with a bleeding tendency

The erythrocyte sedimentation rate is elevated The total serum protein usually is normal but serum albumin is decreased and globulin is increased Electrophoretic studies have disclosed the hyperglobulinemia to be due to an increase in both alpha and gamma globulin When the serum of a patient with this disease is chilled there often is a small amount of protein precipitated so called cryoglobulin (p 1229)

False positive flocculation tests (Hinton Kahn Eagle VDRL) and false positive complement fixation tests (Wassermann) or anticomplementary Wassermann tests are found in nearly one fourth of the cases and can precede the onset of clinical manifestations by many years

It is usual to find red cells white cells and hyaline and granular casts in the urine The demonstration of L E cells establishes the diagnosis of systemic lupus erythematosus When leukocyte or bone marrow suspensions from the patient or from a normal subject are allowed to incubate with plasma or serum from a patient with systemic lupus erythematosus there appear characteristic L E cells in the stained cellular sediment The L E cell is a large polymorphonuclear leukocyte containing an intracellular mass which has the shape but not the staining characteristics of a cell nucleus It has been demonstrated that this homogeneous mass contains depolymerized desoxyribonucleic acid indicating its nuclear origin In the sediment one may also see *tart* cells (histiocytes or polymorphonuclear leukocytes containing a mass identifiable as nuclear material) Other abnormalities include *rosettes* (clusters of granulocytes about a homogeneous mass) and *globs* (free masses of homogeneous material like that seen in the L E cell and identical with the hematoxylin bodies seen in histologic sections from patients with systemic lupus erythematosus) Only the L E cell can be regarded as specific in the diagnosis of systemic lupus erythematosus The exact mechanism for production of the L E cell is not known The plasma or serum factor is present in the gamma globulin fraction of the plasma of patients with this disorder False positive tests for L E cells have been observed to occur in a few patients who have been maintained for long periods on hydralazine (Apresoline) and who have an illness resembling systemic lupus erythematosus In addition positive tests have been obtained with *a few patients with acute sensitivity reactions to* penicillin There is no certainty as to the best procedure for inducing the L E cell phenomenon in vitro It is recognized that patients with this disease may have no demonstrable L E cells When repeated preparations for L E cells are performed in a uniform fashion in a given patient throughout his illness L E cells may decrease or rarely disappear during remissions of the disease that have occurred spontaneously or have been induced by therapy

Diagnosis It is now recognized that systemic lupus erythematosus is not a rare disease Especially in a female the presence of arthritis arthralgia fever or chest pain should suggest its possibility An accompanying typical facial rash will establish the diagnosis Anemia leukopenia slight albuminuria and an abnormal urinary sediment are helpful aids In the absence of possible drug or serum sensitization the diagnosis would be established by demonstrating the presence of L E cells Repeated tests should be made before stopping the search for L E cells In a few instances the diagnosis has been made by finding periarterial fibrosis in a spleen removed from a patient with thrombocytopenic purpura or by the finding of "wire loop" lesions in a needle aspiration biopsy of a kidney Systemic lupus erythematosus resembles many other diseases In particular acute rheumatic fever rheumatoid arthritis subacute bacterial endocarditis glomerulonephritis hemolytic anemia thrombocytopenia and chronic infections such as tuberculosis may simulate this disease

Treatment ACTH and cortisone or related steroids constitute the most effective therapy for this disorder The dosage needed varies with the severity of symptoms and with the type of disturbance that is predominant It has been emphasized that systemic lupus erythematosus is usually a remittent disease Often therapy may be employed only during an acute exacerbation and then be

vesicular and desquamative lesions have also been described Particularly in those patients in whom there is a history of Raynaud s phenomenon there may be sclerodermatous involvement of the fingers hands forearms and face

Edema or erythema of the face trunk or extremities is not infrequent Periorbital edema occurs in many patients The skin about the eyes may have a light purple (heliotrope) hue

Most characteristic is the evidence of muscle involvement Frequently the patients complain of stiffness tenderness decreased strength and easy fatigability of the affected muscles As the disease progresses skeletal muscles of the trunk and proximal portions of the extremities tend to show the greatest involvement Usually one can elicit tenderness by pressure and passive motion Atrophy contractures and calcification may be present

The striated muscles of the eyes pharynx, larynx the diaphragm or the intercostal muscles can be affected giving rise to diplopia dysphagia, hoarseness dyspnea Tachycardia and arrhythmias are the usual findings when the heart is affected Congestive heart failure is rare

In occasional cases one may encounter other manifestations such as tongue and mucous membrane lesions retinal changes lymph node enlargement splenomegaly hemorrhagic tendencies and arthralgia

Patients with dermatomyositis frequently lose weight However other constitutional symptoms are slight Fever is present in fewer than half the patients usually is low grade and tends to be intermittent

A number of patients with dermatomyositis are found to have concomitant malignant tumors Often the symptoms of malignancy are the first to appear The possibility of some type of malignant disease should be considered in every patient with dermatomyositis

Laboratory Findings Slight anemia is frequent The leukocyte count is usually normal In about 50 per cent of patients an increase in eosinophils or monocytes is found in the differential count Often the erythrocyte sedimentation rate is moderately increased There may be a reduction in serum albumin and an increase in serum globulin Proteinuria has been observed but other evidence of renal damage is uncommon

A relatively constant finding in adults is the reduction in the amount of urinary excretion of creatinine per 24 hr in association with a spontaneous creatinuria which may range from 200 to 1 200 mg per 24 hr Moderate daily fluctuations in creatinine excretion occur and variations may be found as the disease alters in severity

The histologic changes in biopsies of affected muscles are almost pathognomonic Occasionally similar changes are observed in the muscles of patients with diffuse scleroderma or systemic lupus erythematosus

Diagnosis The presence of muscle tenderness and muscle atrophy in conjunction with periorbital edema should suggest the diagnosis Helpful laboratory findings are decreased urinary creatinine excretion together with spontaneous creatinuria an increase in monocytes and eosinophils in the stained blood smear and biopsy evidence of muscle lesions

Early psychoneurosis may be suspected As the disease progresses the possibilities include polyarteritis nodosa systemic lupus erythematosus thyrotoxic myopathy peripheral neuritis progressive muscular atrophy myasthenia gravis myositis ossificans trichinosis sarcoidosis pellagra thromboangiitis obliterans and Addison s disease It may be difficult or impossible to differentiate between dermatomyositis and scleroderma until extensive muscle involvement is present A number of observers consider these two disorders to be variants of a single process

Dermatomyositis at times appears to merge with the syndrome *chronic polymyositis* which is considered in the next chapter

Treatment There is no measure which provides uniform success in the treatment of dermatomyositis Aspirin or sodium salicylate often provides relief of pain In a number of instances treatment with ACTH or cortisone or cortisonelike compounds has produced some benefit The details of therapy with these agents are considered in the section on systemic lupus erythematosus

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tients the joints show deformities analogous to those of rheumatoid arthritis Hoarseness may result from changes in the larynx Dysphagia is probably the most frequent gastrointestinal disturbance but there may be epigastric pain nausea or vomiting The chest expansion may be limited by scleroder matous changes in the skin of the thorax and fine interstitial pulmonary fibrosis occurs Fibrous tissue may replace heart muscle and result in cardiac failure In an occasional case of scleroderma rapidly progressive vascular lesions in the kidney are ac companied by severe hypertension and lead to fatal *renal insufficiency* The thickening of the skin may remain localized or the entire body may become implicated Occasionally symptoms such as dys phagia or dyspnea arise from visceral lesions at a time when the changes in the skin are minimal Contractures can lead to invalidism and food intake may be difficult because of limited movement of the jaws The disease can regress spontaneously or become stationary Death attributable specifically to cardiac pulmonary or renal lesions may occur More commonly death results from an intercurrent infection In a number of patients scleroderma remains primarily a disorder of the skin for many years

In the advanced case the characteristic skin induration is easily recognized Early the occur rence of edema arthralgia and vasomotor disturb ances (Raynaud s phenomenon) should lead to consideration of this disease Focal and diffuse scleroderma may be encountered in dermatomyo sitis which is recognized primarily by the associated muscle tenderness Scleredema adultorum (p 1708) may be difficult to distinguish from scleroderma in an early stage There is a rare familial disorder termed *Werner s syndrome* or the closely related *Rothmund syndrome* in which sclerodermatous changes in the extremities are associated with bi lateral juvenile cataracts hypogonadism progeria and a tendency to diabetes mellitus

Laboratory Data The routine blood examination usually shows no abnormality other than an elevated erythrocyte sedimentation rate Frequently there is slight albuminuria The serum albumin is reduced and the serum globulin tends to be increased Sig nificant increases in urinary creatine excretion are found only in those cases where there is muscle alteration identical with that seen in dermatomyo sitis Roentgenograms may show areas of osteo porosis and destructive lesions of the terminal phalanges Likewise changes in the esophagus small bowel colon lung and heart may be dis closed In certain cases *studies with barium demon* strate malfunction of the esophagus even though there may be no complaint of dysphagia The small bowel pattern likewise may be abnormal radiologi cally in the absence of intestinal symptoms Biopsy of the affected skin often discloses the characteristic lesion

Treatment There is no *specific treatment* Cervi codorsal sympathectomy has given temporary bene fit in *selected cases with pronounced* vasomotor disturbances but usually has *not resulted in regres* sion of lesions The judicious use of physiotherapy to prevent and overcome contractures *and to main* tain and to improve muscle strength *seems to be* the most reasonable form of treatment at this time ACTH and cortisone or related steroids *may* be employed in the management of this disease The results of this form of treatment are inconsistent and occasionally the hormones appear to aggravate the process The schedules for hormone therapy considered in the section on treatment of systemic lupus (p 1702) would apply to the management of scleroderma

DERMATOMYOSITIS

Definition This is a chronic often fatal disorder affecting primarily the skin and striated muscle The etiology is unknown Depending upon the manifestations of the disease other names have been applied to it These include *polymyositis dermatomucomyositis neuromyositis* and *poikilo dermatomyositis*

Dermatomyositis has been observed in whites Negroes and Orientals Individuals of any age may be affected but it is most frequent at ages between ten and fifty years There is no sex predominance

Pathology Gross anatomic findings are usually meager One may detect changes in striated mus cles a cutaneous eruption and occasionally lymph node and splenic enlargement The histologic changes in the skin are not characteristic The microscopic findings in the muscle may be diffuse or focal Sometimes they are confined to a segment of a single muscle The muscle fibers show pro liferation of sarcolemmal nuclei occasional giant cells and varying degrees of atrophy necrosis loss of striation hyalinization fragmentation or fatty degeneration A moderate infiltration with lympho cytes and histocytes may be present in interstitial tissue which frequently is increased in amount In the small arteries and arterioles the walls may be thickened and the lumens narrowed

Rarely changes similar to those occurring in skeletal muscle are present in the myocardium Perineural cellular infiltrations have been observed

Clinical Manifestations The onset is insidious Not infrequently a recent upper respiratory infec *tion precedes the earliest symptoms* Patchy ery thema or edema myalgia or vasomotor disturbances may be presenting symptoms

The skin manifestations are extremely diverse Most common are erythematous eruptions Purpuric

in establishing the diagnosis A decrease in the mean duration of the action potential appears to be one of the more common disturbances The absence of fibrillation potentials helps to differentiate it from spinal muscular atrophy and lesions of the peripheral nerves (see p 504)

The diagnosis of chronic polymyositis is difficult when there is weakness without any atrophy or change in consistency of muscles Whenever the weakness is symmetrical and predominantly proximal in the extremities this disorder should be considered

It should be evident that some cases of chronic polymyositis do not differ significantly from instances of dermatomyositis However other cases of polymyositis bear only slight resemblance to the latter It is not unusual for these patients to be labeled as having muscular dystrophy progressive muscular atrophy polyneuritis or hysteria A few cases have been described in which enlargement of the calf muscles appeared in connection with polymyositis in children making difficult the distinction between muscular dystrophy and polymyositis Suitable biopsies of the affected muscles will usually clarify the situation

More than half the cases of chronic polymyositis improve after treatment with ACTH or cortisone and related compounds The manner of therapy described in the section on systemic lupus erythematosus may be consulted It is important to recognize that response to therapy may be delayed in this disorder Treatment should be continued for 2 or 3 months before an attempt to evaluate its efficacy

WEGENER S GRANULOMATOSIS

The rare disease Wegener's granulomatosis has certain clinical and pathologic similarities to polyarteritis nodosa It affects both sexes equally and persons of all ages are susceptible In the diffuse form of the disease the major pathologic changes are found in the respiratory tract and kidneys Most characteristic are necrotizing granulomas in the lung or in ulcerated lesions of the upper respiratory tract (nose sinuses pharynx) Vasculitis of pulmonary arteries and veins is almost a constant feature Both vasculitis and granulomas may be widely distributed throughout the body In the kidneys there is a focal glomerulitis giving rise to necrosis of portions of glomerular tufts Other glomeruli may show epithelial crescents

Clinically this disease should be suspected when ulcerated lesions of the upper respiratory tract are found in persons in whom no other etiology seems likely Cough and pulmonary infiltrations may be the initial findings Fever and loss of weight are prominent Other symptoms and signs depend upon the distribution of the vascular and granulomatous lesions Anemia and leukocytosis are usual findings Transient eosinophilia is common The urine may contain protein red blood cells leukocytes and casts There may be hyperglobulinemia

There is no known treatment for this disease Because some cases seem to result from hypersensitivity ACTH and adrenal steroids have been tried with equivocal results

Death from secondary bacterial infection or from renal insufficiency is frequent

WEBER CHRISTIAN DISEASE

Introduction Weber Christian disease or relapsing febrile nodular nonsuppurative panniculitis is a disorder characterized by recurrent bouts of fever and crops of subcutaneous nodules resulting from focal necrosis of fatty tissue This disease is three times as common in females as in males Most cases are observed in individuals between the ages of twenty and forty

Manifestations Most striking is the tendency of this disease to exacerbations and long remissions Fever usually appears with the onset of skin manifestations The duration and magnitude of the fever are variable The subcutaneous lesions are freely movable raised and tender and there is erythema of the overlying skin Usually the lesions are less than 1 cm in diameter but they coalesce to form larger lesions They are most common on the thighs but may occur on the trunk and upper extremities With healing depression of the skin frequently is observed The nodules consist of necrotic fatty tissue infiltrated with lymphocytes plasma cells and fat laden macrophages Foreign body giant cells are often present Occasionally small vessels (arteries and veins) show leukocytic infiltration

The fever and cutaneous manifestations may appear disappear for intervals of months or years and then recur The disease may continue for 10 years During the febrile periods the leukocyte count may be normal elevated or depressed In patients with leukopenia splenomegaly is sometimes present Occasionally there is a mild anemia

Biopsy wounds are prone to heal slowly A few patients have died as a result of the disease Autopsy studies have shown fatty metamorphoses with central necrosis in liver lobules Characteristic granulomatous lesions have been encountered in the fat surrounding the trachea the pericardium the pancreas adrenals kidneys the mesentery omentum and bone marrow

Diagnosis Recurrent fever subcutaneous nodules and the biopsy findings should establish the diagnosis The cutaneous lesions may be difficult to differentiate morphologically from the lesions of

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B V Jager

CHRONIC POLYMYOSITIS

This affliction of muscle may appear at any age. It is perhaps most frequently observed to begin in the first to fourth decades There is no sex predominance Apart from low grade fever and loss of weight constitutional symptoms are slight Occasionally there is mild dysphagia A few patients have Raynaud s phenomenon Early in the illness there may be aching or tenderness of the muscles

Most often it is the symmetrical changes in the muscles of the pelvic girdle and thighs which produce the earliest symptom of weakness This may lead to difficulty in climbing stairs or in rising from a sitting position Subsequently the muscles of the upper arm and shoulder girdle become involved In certain instances the weakness is first noted in this region As the disease continues there may be obvious fibrosis and atrophy of muscles Weakness may be marked at a time while the muscle mass is still normal in consistency and in amount In some patients the process extends to affect nearly all of the skeletal muscles

The course is highly variable Often it is insidiously chronic and progressive or it may be a smoldering process which is interrupted by episodes of intense activity followed by a return to a gradual course Spontaneous remissions usually incomplete are frequent The process may stabilize in such a remission with only a limited degree of localized muscle weakness as a residual

Upon biopsy the affected muscles demonstrate changes which do not differ significantly from those of dermatomyositis

A few of these patients have a relative and an absolute increase in eosinophilic leukocytes The blood otherwise usually is unremarkable and the urine examination is negative These patients show varying degrees of creatinuria in addition to a reduction in urinary creatinine The amount of creatine in the urine may not exceed the value for normal subjects but usually it is increased

A number of electromyographic abnormalities have been observed in polymyositis When multiple sites are examined the observations can be helpful

histologic confirmation of this diagnosis but also gives relief of discomfort ACTH and cortisone may be effective in relieving the symptoms Therapy with these agents should be maintained for a number of weeks since exacerbations often are observed when this form of treatment is employed for brief periods and then is discontinued

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264 THE ERYTHEMAS

B V Jager

This chapter contains a brief description of erythema multiforme erythema multiforme exudativum erythema nodosum erythema induratum and nodular vasculitis Perhaps hypersensitivity reactions are responsible for all of these disorders

ERYTHEMA MULTIFORME

Erythema multiforme is a symmetrical eruption which is thought to represent an allergic response to drugs or to bacterial infections The skin lesions may be macular papular or vesicular in character The distribution is varied but frequently the wrists backs of the hands lower legs and dorsal aspects of the feet are affected The mucous membranes are implicated in many instances so that erythematous and vesicular lesions may be encountered on the lips in the mouth and pharynx, and occasionally in the genital region There is usually local discomfort at the site of the lesions Occasionally there is a concomitant systemic reaction with fever and arthralgia The appearance of the eruption varies and it may be confused with many other types of dermatologic disorders

In some instances of acute rheumatic fever a cutaneous eruption termed *erythema marginatum* is present Here there are red elevated flat topped lesions These usually enlarge peripherally and may vary from pink to violet in color

Another type of erythema multiforme is termed the *iris* variety These lesions are vesicopapules which spread peripherally forming rings of various sizes and shapes The margins are often highly colored giving the lesion the appearance of a target

The duration of the cutaneous lesions seldom exceeds 4 weeks Recurrences may appear long after disappearance of the original skin rash

Usually no therapy is indicated Effort should be made to determine if any drug sensitization is responsible for the difficulty Such a drug should not be given to the patient at a future time For more severe cases there may be improvement with use of any one of the following in suitable dosage

sarcoid erythema induratum (Bazin's disease) nodular vasculitis local thrombophlebitis and erythema nodosum In diffuse symmetrical lipomatosis and in adiposis dolorosa the subcutaneous indurations sometimes are similar to those seen in Weber Christian disease

Treatment Sulfonamides and antibiotics are of no benefit Cortisone prednisone prednisolone or ACTH in some cases produce symptomatic relief with disappearance of fever and cutaneous nodules The treatment program described in the section on lupus erythematosus may be employed

SCLEREDEMA ADULTORUM

Introduction Scleredema adultorum is a rare disorder which occurs more often in females than in males It may appear at any age but is most frequent in the third decade It is a benign self limited disease characterized by edema and induration of the skin Scleredema was described by Buschke in 1902 and previously by Piffard in 1876 who termed the disorder *sclerasis*

Clinical Manifestations In the majority of cases there is a history of a beta hemolytic streptococcal infection 1 to 3 weeks preceding the disease Usually the onset is characterized by edema which begins in the neck and progresses over 1 to 3 weeks to involve the face trunk upper extremities and sometimes the lower extremities The hands and feet are not affected Occasionally there is an erythematous eruption at the onset The tongue and skeletal muscle may be implicated Effusions into joints or pleural space have been observed

The skin of involved regions usually retains its normal appearance but may be pale and indurated There are no changes in pigmentation Histologically sections of skin show swelling of the collagen bundles of the corium These bundles may be separated by clear spaces the contents of which sometimes are stainable with the dye cresyl violet

No abnormalities are found on laboratory examination The duration of the disease is variable It may last a few months to several years Complete recovery is the rule

Diagnosis The history of the preceding respiratory infection the finding of induration of the skin neck shoulders and upper arms—with sparing of the hands—and the absence of laboratory abnormalities should suggest the diagnosis At times this disorder may be confused with the early stages of diffuse scleroderma In scleroderma however there may be pigmentation or depigmentation of the skin vasomotor disturbances and involvement of the hands Scleredema may be confused with dermatomyositis in the early stages but the course of the two diseases is distinct

TEMPORAL ARTERITIS

Temporal arteritis also called *cranial arteritis* or *giant cell arteritis* is a vascular disease affecting branches of the carotid arteries of persons beyond the age of fifty five years Clinically the temporal artery is usually prominently involved Both sexes are equally vulnerable to this uncommon affliction which is self limited with recovery to be anticipated within 2 to 12 months

The affected arteries have narrowed lumens which occasionally are occluded by thrombi Rarely there are aneurysmal dilatations of arteries Histologically the vessels show a striking concentric proliferation of fibroblasts in the intima It is this feature which often results in a great reduction in the size of the lumen Much of the muscle and elastic tissue of the media is destroyed There may be fibrinoid necrosis in this area Also in the media there is an infiltration with histiocytes and large giant cells of the foreign body type Post mortem examinations on affected subjects have disclosed that the arterial lesions can be more disseminated than would be expected from clinical observations Characteristic histologic lesions can occur in the following arteries the aorta the innominate internal and external carotid subclavian vertebral temporal ophthalmic pulmonary coronary celiac renal iliac and popliteal

There often are mild systemic symptoms prior to and during the course of this illness These include low grade fever malaise anorexia loss of weight and aching of muscles and joints Most patients complain of excruciating headache localized to one or both temporal regions This is followed by redness and heat of the skin overlying the tender temporal artery The pulsations of this vessel initially present decrease and usually disappear as the disease progresses Ischemia in various areas arising from the intimal proliferation accounts for many of the later manifestations About one third of the patients develop impaired vision in one or both eyes This may result in total and permanent blindness There may be tinnitus and vertigo Reduction in hearing may appear early in the illness and then persist after recovery from the systemic illness Thrombosis of other branches of the internal carotid and vertebral arteries can result in extensive brain injury Ulcerations may appear in the skin along the temporal vessels or in the nose and mouth Rarely there are palpable aneurysms in the neck or chest

Laboratory studies usually will disclose slight anemia an elevated sedimentation rate and moderate leukocytosis

Various forms of therapy for this disorder have been attempted Section of the painful temporal artery not only provides a segment of vessel for

loma venereum (p 1096) It has been observed in *trichophytosis leprosy (p 954)* Carrion s disease (p 915) and other infections Erythema nodosum occasionally is present in sarcoidosis It also may be associated with drug hypersensitivity reactions Many instances were observed when sulfathiazole was used extensively Frequently no etiologic fac tor can be detected

Pathologically the lesions are remarkably similar in appearance in spite of the diversified agents that may elicit their appearance The well developed lesion consists histologically of granulomas of histio cytes lymphocytes and foreign body giant cells in the subcutaneous connective tissue and fat There often are fibrinoid changes in the collagen and the vessels may show mild inflammatory changes Leukocytes in the walls of small arteries and venules may suggest the diagnosis of polyarteritis nodosa (p 1698)

The characteristic skin lesion of erythema nodosum is a raised tender erythematous nodule on the lower extremities The lesions usually are ovoid and vary from 1 to 5 cm in diameter It is common for several lesions to be present simul taneously Usually these appear at different times during the illness As the lesions persist the over lying skin initially red becomes blue or brown suggesting a bruise

Fever arthralgia and *arthritis* are common associated findings Occasionally there are purpuric lesions The illness usually lasts 1 to 3 weeks but may be longer After intervals of months or years the condition may recur

Laboratory studies usually show an elevated erythrocyte sedimentation rate and a moderate leukocytosis Eosinophilia is uncommon except in coccidioidomycosis Albuminuria during the acute stage is frequent Roentgenograms of the chest taken late in the illness often show considerable degrees of hilar adenopathy

The diagnosis of this disorder usually is not dif ficult Occasionally it may be confused with nodular panniculitis (Weber Christian disease p 1707) nodular vasculitis and erythema induratum

Usually no specific treatment is indicated In severe or long lasting illness good responses may be expected when ACTH or cortisone or related steroids are given for periods of several weeks in adequate doses

ERYTHEMA INDURATUM (Bazin s Disease)

Erythema induratum is thought to represent a focal cutaneous or subcutaneous tuberculous infec tion in which hypersensitivity to products of the tubercle bacilli may have a role The affected sub jects usually are females below the age of thirty years The skin lesions are to be found on the legs below the knees They begin as soft and often tender subcutaneous infiltrates with red or purple discoloration of the overlying skin Later there may be induration of the nodules with attachment to the skin The nodules tend to persist for long periods and may ulcerate or may undergo spon taneous absorption Healing of both ulcerated and nonulcerated lesions often is accompanied by scar ring pigmentation and depression of the overlying skin

The nodules tend to recur over long periods There often is very little systemic reaction with the skin changes Most individuals with this disorder *display extremely severe cutaneous reactions to* tuberculin

Pathologically sections of the nodules may re veal typical tubercles caseation necrosis fibrosis lymphocytic infiltration and vasculitis of arteries and veins Occasionally no typical tubercles are to be seen Tubercle bacilli should be demonstrated either by stains of histologic sections or by culture or inoculation of guinea pigs with portions of the nodule removed at biopsy If bacteriologic and his tologic proof of tuberculosis is lacking a specific diagnosis of erythema induratum is not justified Erythema nodosum Weber Christian disease and nodular vasculitis are considered in the differential diagnosis

Antituberculous therapy with isoniazid strepto mycin or para aminosalicylic acid is indicated when the diagnosis is established Response to therapy often requires many months

NODULAR VASCULITIS

Females in the age range of thirty to fifty years seem to be particularly disposed to this disorder Some of them have been found to have evidence of vascular disease such as acrocyanosis Raynaud s phenomenon or mild hypertension The lesions of nodular vasculitis usually are confined to the legs below the knees Often both legs are affected at the same time The nodules appear in crops of four or five They persist for a number of weeks and then disappear for a period of several months only to recur The nodules are raised tender and are red or purple Some undergo ulceration but most heal with residual scarring pigmentation and de pression of the skin Often they produce consid erable discomfort

Pathologically the typical nodules show vascu litis of arteries and veins fibrosis and infiltration with lymphocytes histiocytes and foreign body giant cells There are no typical tubercles

It should be evident that nodular vasculitis has a close clinical and pathologic similarity to erythema induratum Often they cannot be distinguished unless tubercle bacilli are demonstrated Clinically

ACTH cortisone hydrocortisone prednisone and prednisolone

ERYTHEMA MULTIFORME EXUDATIVUM

Erythema multiforme exudativum is a disorder of varying severity affecting the skin eyes oral cavity and genital region It is thought to include diseases designated as *Hebra s disease Stevens Johnson syndrome Klauder s disease* ectodermosis erosiva pluriorificialis dermatostomatitis and perhaps Behcet s syndrome

The *etiology* is unknown In a few instances *sensitivity to* sulfonamides or other drugs may have been responsible It has been suggested that a virus is *the* causative agent but convincing proof is lacking Males are affected five times as frequently as *females* The majority of cases appear during the first three decades of life This disease is more com*mon in the* winter and spring

The *onset* usually is abrupt and is associated with chills fever headache and sore throat Conjunctivitis and stomatitis soon ensue Later there may be genital lesions and various types of skin eruptions Bronchopneumonia may occur There frequently is arthralgia but swelling of joints is uncommon The duration of the disorder is highly variable but the usual course is 2 to 8 weeks Recurrences are frequent and may be spaced at short intervals or several months to several years apart Permanent blindness may develop following corneal ulcerations

The *skin lesions* commonly affect the hands and feet but may involve the entire body the scalp usually being spared Palmar and plantar lesions are relatively common The lesions may be erythematous purpuric vesicular or bullous The papular erythematosus lesions often assume a purple hue and may be circular with uninvolved central portions (*erythema iris*) or may be serpiginous (*erythema gyratum*) The vesicles and bullae after rupture usually become crusted and hemorrhagic Often new crops of skin eruptions appear during the illness varied stages of their development being present simultaneously

The earliest *mouth lesions* are vesicular Later these rupture and a diffuse membranous stomatitis results The lips usually are swollen ulcerated and covered with hemorrhagic crusts Swallowing of fluid or food may be impossible

In the eyes there is a diffuse conjunctivitis with edema of the lids Corneal ulcerations may appear and lead to subsequent ophthalmitis and blindness Iritis may be present in the absence of corneal ulceration

Ulcerations of the scrotum and the glans penis are not infrequent There may be an associated urethritis In females the genital lesions are represented by a vulvovaginitis Occasionally ulcers appear in the perianal region

Clinical and radiologic evidence of pulmonary infiltration is relatively common

The blood examination frequently is normal There may be leukocytosis or rarely leukopenia Occasionally there is an absolute eosinophilia During the febrile period albuminuria often is present

Not all patients with this syndrome present all of the manifestations described above Moreover the severity of the disease varies greatly from person to person The diagnosis is established by the presence of a profound systemic reaction in addition to eye mouth skin and genital lesions

The *differential diagnosis* would include human infection with hoof and mouth virus (p 1104) chickenpox (p 1058) acute pemphigus and smallpox (p 1060) A biopsy of the skin usually will be sufficiently characteristic as to distinguish between pemphigus and the disorder under consideration The mouth lesions may simulate Vincent s angina or diphtheria Reiter s syndrome (p 1154) has many of the features of erythema multiforme exudativum However joint involvement is usually severe in Reiter s disease whereas it is minimal or absent in the syndrome under consideration here

Treatment is unsatisfactory Various antibiotics have been employed They should be useful in combating secondary infections when these are present In a number of instances benefit results from administration of ACTH or of cortisone and related steroids Use of these agents as outlined under Systemic Lupus Erythematosus (p 1702) deserves further trial since this disease in a severe form or with secondary infections may have a fatal outcome

ERYTHEMA NODOSUM

Erythema nodosum is a brief febrile illness characterized by cutaneous painful nodules—commonly on the legs—arthralgia or arthritis and malaise It generally is regarded as a reaction of hypersensitivity to a variety of agents In North America it most frequently follows in the wake of *group A beta hemolytic streptococcal infections* This is supported by historical evidence of antecedent pharyngitis the frequent presence of streptococci in the throat the commonly elevated antistreptolysin O titer and the observation that killed streptococci injected into subjects with this disorder elicit greater febrile and local reactions than in normal subjects In the Southwestern part of the United States erythema nodosum commonly is associated with primary coccidioidomycosis (p 988) This disorder may also occur early in tuberculosis and at the time when the tuberculin test has become positive Similarly it may appear in lymphogranu

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Laboratory studies usually show an elevated erythrocyte sedimentation rate and a moderate leukocytosis Eosinophilia is uncommon except in coccidioidomycosis *Albuminuria during the acute* stage is frequent Roentgenograms of the chest taken late in the illness often show considerable degrees of hilar adenopathy

The diagnosis of this disorder usually is not difficult Occasionally it may be confused with nodular panniculitis (Weber Christian disease p 1707) nodular vasculitis and erythema induratum

Usually no specific treatment is indicated In severe or long lasting illness good responses may be expected when ACTH or cortisone or related steroids are given for periods of several weeks in adequate doses

ERYTHEMA INDURATUM (Bazin's Disease)

Erythema induratum is thought to represent a focal cutaneous or subcutaneous tuberculous infection in which hypersensitivity to products of the tubercle bacilli may have a role The affected subjects usually are females below the age of thirty years The skin lesions are to be found on the legs below the knees They begin as soft and often tender subcutaneous infiltrates with red or purple discoloration of the overlying skin Later there may be induration *of the nodules with attachment to* the skin The nodules tend to persist for long periods and may ulcerate or may undergo spontaneous absorption Healing of both ulcerated and nonulcerated lesions often is accompanied by scar*ring pigmentation and depression of the overlying* skin

The nodules tend to recur over long periods There often is very little systemic reaction with the skin changes Most individuals with this disorder display extremely severe cutaneous reactions to tuberculin

Pathologically sections of the nodules may reveal typical tubercles caseation necrosis fibrosis lymphocytic infiltration and vasculitis of arteries and veins Occasionally no typical tubercles are to be seen Tubercle bacilli should be demonstrated either by stains of histologic sections or by culture or inoculation of guinea pigs with portions of the nodule removed at biopsy If bacteriologic and histologic proof of tuberculosis is lacking a specific diagnosis of erythema induratum is not justified *Erythema nodosum* Weber *Christian disease* and nodular vasculitis are considered in the differential diagnosis

Antituberculous therapy with isoniazid streptomycin or para aminosalicylic acid is indicated when the diagnosis is established Response to therapy often requires many months

NODULAR VASCULITIS

Females in the age range of thirty to fifty years *seem to be particularly disposed to this disorder* Some of them have been found to have evidence of vascular disease such as acrocyanosis Raynaud's phenomenon or mild hypertension The lesions of nodular vasculitis usually are confined to the legs below the knees Often both legs are affected at the same time The nodules appear in crops of four or five They persist for a number of weeks and then disappear for a period of several months only to recur The nodules are raised tender and are red or purple Some undergo ulceration but most heal with residual scarring pigmentation and depression of the skin Often they produce considerable discomfort

Pathologically the typical nodules show vasculitis of arteries and veins fibrosis and infiltration with lymphocytes histiocytes and foreign body giant cells There are no typical tubercles

It should be evident that nodular vasculitis has a close clinical and pathologic similarity to erythema induratum Often they cannot be distinguished unless tubercle bacilli are demonstrated Clinically

nodular vasculitis tends to occur in a slightly older age group the lesions tend to be smaller and they are less likely to ulcerate than those of erythema induratum

ACTH or cortisone and related compounds often lead to disappearance of skin lesions in nodular vasculitis

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265 DISORDERS OF THE JOINTS

Laurence E Shulman and Joseph J Bunim

Terms used to designate abnormal conditions of the joints are numerous frequently ambiguous and only too often used interchangeably *Rheumatism* is derived from the Greek *rheumatismos* this was believed to be an evil humor originating in the brain and flowing to the joints where it produced pain Currently rheumatism is used most as a generic term often loosely to indicate pain stiffness or deformity of joints muscles and related structures The *rheumatic diseases* embrace a large group of diseases of the musculoskeletal system in which alterations take place in the articular structures (synovial tissue joint capsule cartilage and bone) and/or in the connective tissue surrounding the joints as in tendons or in various other organs of the body Because of the prominent involvement of this tissue in these disorders it is becoming more fashionable and rightly so to designate them *diseases of connective tissue* The term *arthritis* is usually used to denote any disorder of joints although more properly its use should be restricted to those disorders of joints which are inflamed A joint disorder not accompanied by inflammation is frequently called an *arthropathy* If however the pain tenderness or stiffness originates from a nonarticular structure such as muscle tendon ligament bursa or subcutaneous fat the condition is often labeled *fibrositis* Wherever possible more specific terminology such as *tendinitis bursitis* or *panniculitis* should be used

Prevalence Surveys conducted by the Public Health Service show that over 10 million persons suffer from some form of rheumatism indicating that it is one of the most common causes of chronic illness in the United States Rheumatic disorders rank second to nervous and mental diseases as causes of temporary and permanent disability Of the 10 million people with rheumatic complaints almost one half or 4 5 million have arthritis over 10 per cent or 1 143 000 are partially disabled and almost 2 per cent 190 000 are completely disabled More than half the disabled are under forty five years of age One quarter of the 10 million changed their jobs presumably because of their rheumatic symptoms In other countries the toll from rheumatism is even greater In Great Britain for example half the population suffers from nondisabling rheumatism 7 per cent are incapacitated by it for at least 1 day each year and one sixth of the total industrial disability is ascribed to rheumatism Similarly in Switzerland arthritis is

responsible for 16 per cent of all sickness reports to insurance companies and the same proportion of total absence from work. Among the major categories of chronic disease rheumatism cripples most and kills least. Much of the crippling occurs in young people during their productive years. The economic loss and personal unhappiness which result make rheumatism a national health problem.

Classification

Difficulties arise when one attempts to set up a workable and logical classification of joint diseases. It cannot be constructed satisfactorily on etiologic grounds when the cause of so many forms of joint disease is unknown. Separation on the basis of pathologic change is often helpful, yet it may actually restrict knowledge, since the connective tissues are capable of reacting to injurious stimuli in only a limited number of ways. Differentiation on clinical grounds alone may be similarly unsatisfactory because widely divergent pathologic forces may give rise to an identical clinical picture. Division into acute and chronic categories is also hazardous because acute arthritides may become chronic, and chronic arthritides may begin acutely or have acute exacerbations.

Thus it is clear that the state of our knowledge or lack of it permits no complete or satisfactory classification. Most attempts at clarifying joint diseases include etiologic, pathologic and clinical factors. The American Rheumatism Association has approved a classification which conforms to the phraseology of "The Standard Nomenclature of Disease," thus providing uniformity. Wherever possible its use is recommended. The accompanying outline (Table 134), however, is offered as a more useful guide to differential diagnosis because it is based largely on pathogenetic features.

Approach to the Patient with Joint Disease

Every effort should be made to establish an accurate and precise diagnosis in patients with joint complaints. This is essential for proper management.

History. The *age* of the patient is not as important in diagnosis as was formerly thought. In the elderly, arthritis was assumed to be degenerative joint disease; in the young or middle aged, rheumatoid arthritis. Actually the chance of a person's having rheumatoid arthritis increases up to the age of fifty-five years, after which it remains stationary; conversely, degenerative joint disease can begin as early as the second decade.

Females are more likely to have Heberden's nodes (10:1), systemic lupus erythematosus (8:1) or peripheral rheumatoid arthritis (2:1), whereas rheumatoid spondylitis is decidedly more common in men (9:1).

It is important to know the *occupation* and *avocations* of the arthritic patient. Injury at work or at play gives rise to such conditions as "housemaid's knee," "nurse's feet," "boxer's bursitis," "student's elbow," "baseball fingers" and "weaver's bottom." Trauma can also play an important role in the selection of the sites affected in degenerative joint disease.

Careful attention must also be paid to the *family history*. The family incidence of gout varies from 10 to 18 per cent. Moreover, 25 per cent of the nongouty relatives of patients with gout have hyperuricemia. Another illustration is the familial nature of idiopathic Heberden's nodes, which is also controlled by a single autosomal gene; in this case it is dominant in the female and recessive in the male.

"Growing pains" in childhood may direct one's attention to rheumatic fever or juvenile rheumatoid arthritis. Repeated throat infections, especially if known to be caused by the beta hemolytic streptococcus, also point to rheumatic fever. A history of unexplained fever, skin disorders, serositis and hematologic abnormalities may suggest that the arthritis is merely one manifestation of a collagen vascular disorder. Urethritis may precede arthritis and conjunctivitis in Reiter's syndrome or gonorrhea. At times renal calculi may appear before gouty arthritis. Nephritis may antedate arthralgia in systemic lupus erythematosus. Clearly, a history of trauma to a joint or arthritis in the remote past must be sought, because such an event may be related to the present rheumatic illness.

Meticulous inquiry into *events immediately preceding the onset* of the arthritis yields important clues to diagnosis. An antecedent infection of one or more organs, especially if accompanied by bacteremia, indicates that the arthritis may be infectious. Streptococcal tonsillitis or pharyngitis preceding the arthritis by 1 to 4 weeks strongly suggests rheumatic fever. Prior injections of penicillin or foreign protein, especially if accompanied by fever or urticaria, bring to mind the arthritis of serum sickness. Frequently rheumatoid arthritis is preceded by overwork, emotional stress or exposure to a cold damp environment and is ushered in by constitutional symptoms—feverishness, malaise, fatigability, anorexia, parasthesias and weight loss. Such constitutional symptoms do not antedate the onset of degenerative joint disease.

The *mode of onset* of the arthritis should be ascertained. A joint disorder may appear explosively (as in rheumatic fever), subacutely (as in rheumatoid arthritis) or insidiously (as in degenerative joint disease). There are many exceptions, however

Table 134 CLASSIFICATION OF DISORDERS OF JOINTS

I Arthritis caused by specific infection
- *A* Pyogenic arthritis
  - 1 Staphylococcus
  - Streptococcus
  - 3 Pneumococcus
  - 4 Gonococcus
  - 5 Meningococcus
- *B* Brucellosis (arthritis rare arthralgia common)
- *C* Tuberculosis
  - 1 Arthritis
  - 2 Spondylitis (Pott s disease)
- *D* Syphilis
  - 1 Congenital
    - Symmetrical synovitis (Clutton joints)
    - *b* Osteochondritis (Parrot s pseudoparalysis)
  - Acquired (tertiary)
    - Synovitis
    - *b* Gummatous
- *E* Less common forms of infectious arthritides
  - 1 Bacteria
  - 2 Fungi
  - 3 Viruses

II Arthritis possibly caused by specific infection
- *A* Reiter s syndrome

III Arthritis as a sequel to specific infection
- *A* Rheumatic fever

IV Arthritis caused by hypersensitivity to foreign agent
- *A* Drug reactions
- *B* Serum sickness
- *C* Anaphylactoid purpura

V Arthritis in widespread inflammatory connective tissue disease cause unknown
- *A* Rheumatoid arthritis and variants
  - 1 Adult peripheral type
  - 2 Juvenile rheumatoid arthritis (Still disease)
  - 3 Rheumatoid spondylitis (Marie-Strümpell disease)
  - 4 Psoriatic arthritis
  - 5 Felty syndrome
  - 6 Arthritis with ulcerative colitis
  - Sjögren syndrome
- *B* Collagen vascular disorders
  - 1 Systemic (disseminated) lupus erythematosus
  - Polyarteritis (periarteritis nodosa)
  - 3 Progressive systemic sclerosis (scleroderma)
  - 4 Dermatomyositis
- *C* Granulomatous
  - 1 Sarcoidosis
  - 2 Erythema nodosum

VI Arthritis caused by metabolic or endocrine disorders
- *A* Gout
- *B* Ochronosis
- *C* Acromegaly

VII Degenerative joint disease (osteoarthritis)
- *A* Generalized
- *B* Localized
  - 1 Hereditary (such as Heberden s nodes)
  - 2 Secondary to previous trauma or infection
  - 3 Secondary to faulty body mechanics
  - 4 Unknown cause

VIII Arthritis caused by trauma to joints
- *A* Direct trauma
- *B* Internal mechanical derangement of joint

IX Neurogenic arthropathy (Charcot joint)
- *A* Tabes dorsalis
- *B* Syringomyelia
- *C* Neuropathy of diabetes mellitus
- *D* *Peripheral nerve injuries*
- *E* Leprosy

X Arthritis caused by bleeding into joints
- *A* Direct trauma
- *B* *Disorders of blood coagulation*
  - 1 Hemophilia and variants

XI Neoplasm of joints
- *A* Cyst
- *B* Lipoma
- *C* Hemangioma
- *D* Synovioma
- *E* Giant cell tumor

XII Arthritis secondary to lesions of bone
- *A* Aseptic necrosis of bone
  - 1 Primary of unknown cause
  - 2 Secondary to
    - *a* Trauma
    - *b* Vascular occlusion
- *B* Neoplasms of bone
  - 1 Primary
  - Metastatic to bone
- *C* Osteochondromatosis
- *D* Osteochondritis dissecans
- *E* Endocrine diseases of bone

XIII Hypertrophic osteoarthropathy

XIV Miscellaneous arthritis
- *A* Shoulder hand syndrome
- *B* Palindromic rheumatism
- *C* Intermittent hydrarthrosis
- *D* Psychogenic rheumatism (hysterical arthritis)

XV Periarticular conditions (*nonarticular rheumatism*)
- *A* Fibrositis
- *B* Tendonitis
- *C* Bursitis
- *D* Tendon sheath cyst (ganglion)
- *E* Myositis
- *F* Neuritis
- *G* Panniculitis

and the interpretation by patients of the acuteness of an illness varies greatly

It is also important to obtain a full characterization of the patient s joint *pain* The pain of acute gouty arthritis for example is constant severe boring and *not influenced by position or time of day* In contrast the discomfort in degenerative joint disease is usually transient mild and superficial it emerges with attempted movement after a period of rest in one position and disappears readily after brief exercise In a different manner the patient with rheumatoid arthritis complains of morning stiffness which disappears gradually only after several hours of activity whereas the pains in the affected joints may become more severe as the day progresses Similarly pain from trauma or deformities may increase as the day wears on

The patient should also be asked about the occurrence of other signs which reflect articular inflammation namely *excessive heat discoloration of the skin tenderness* or *swelling* of the involved joint One must determine whether the swelling is confined to one or more joints near joints but not in them or spread more diffusely

Valuable diagnostic information may come from ascertaining which joint was first involved i e the proximal interphalangeal joint in rheumatoid arthritis the sacroiliac in rheumatoid spondylitis the

istal interphalangeal in degenerative joint disease the great toe in gout or the shoulder in bursitis One should find out whether the arthritis is *migratory* and if it is the *nature of its spread* In degenerative joint disease for example the sites of arthritic symptoms do not tend to change whereas migration of the arthritis is characteristic of rheumatic fever where it is rapid and transient and of rheumatoid arthritis where it tends to be slower and additive Rheumatoid arthritis is noted for the *symmetry* of involvement of joints

The *course* of the disease may provide additional diagnostic clues Acute exacerbations with complete remissions are characteristic of intermittent hydrarthrosis where the flare ups occur regularly and of the early stage of gout where they occur irregularly Over all progression with partial remissions is the most common course in rheumatoid arthritis whereas in degenerative joint disease the illness is usually static or slowly progressive

The presence and extent of *deformities* and the *functional capacity* of the patient may also aid in diagnosis Some disorders such as rheumatoid arthritis are notoriously deforming and crippling others such as rheumatic fever produce no residual articular disability

The details of *previous management and its effect* should be carefully recorded The daily dosage and duration of administration of a given agent are important for the program may not have been sufficient to constitute a valid therapeutic trial An illustration of the potential usefulness of knowing the previous response to therapy is in so called "psychogenic rheumatism" where the diagnosis is said to be confirmed by a reportedly complete lack of response to salicylates or physical therapy

Physical Examination All accessible joints should be systematically and meticulously examined for heat or discoloration of the overlying skin swelling tenderness limitation of motion deformity and crepitation The *temperature* and *color* of the skin proximal and distal to the joint should be compared with those over the joint *Swelling* of the joint may result from one or more of the following pathologic conditions (1) the accumulation within the joint space of fluid demonstrable by fluctuation as in the "patellar click" (2) thickening of the soft tissue (synovia capsule ligament or adipose tissue) in which case there is no fluctuation (3) localized periarticular effusion in a tendon sheath or a bursa (4) diffuse periarticular subcutaneous edema or (5) bony enlargement as in acromegaly tumors of bone or the osteophytes of degenerative joint disease One must be sure that the joint is really enlarged since atrophic muscles may falsely give the impression of joint swelling The degree of *tenderness* should be recorded and subsequently interpreted with the help of the sensory examination and an evaluation of the emotional state of the patient

Limitation of motion of a joint may result from (1) sufficiently painful inflammation to cause muscular spasm or guarding (2) effusions large enough to distend the capsule tightly (3) fibrosis of the capsule (4) fibrosis across the joint space from one synovial surface to another (fibrous ankylosis) (5) bony bridging across the space (bony ankylosis) or (6) various disorders of tendon muscle or nerve One should try to determine whether the *deformity* results from effusion or pain and thus is possibly reversible or from irreversible destruction of joint structures

Crepitation a grating feeling or noise results from the rubbing together of opposing joint surfaces on motion of the joint The character of the crepitation varies with the joint disorder fine or rubbing in rheumatoid arthritis where the abrasive surface is villous granulation tissue coarse or "crunching from the osteophytes and disorganized cartilage in degenerative joint disease These forms of crepitation should be distinguished from "cracking" or "snapping which is caused by slipping tendons over bony prominences

A few instruments are available for quantitating the degree of disability of joints and related structures Simplest and perhaps most important is a tape measure with which the circumference of large joints and certain muscle groups is recorded It should also be used to measure the chest expansion in patients with rheumatoid spondylitis A jeweler s ring sizer can determine the size of the smaller joints of the fingers and toes A dynamometer is used to record grip strength the range of motion of a joint can be ascertained with a goniometer These instruments are useful in following the course of the patient s illness and particularly in studies designed to test the efficacy of a therapeutic agent

The *functional capacity* of the patient with special reference to tasks performed by the extremities should also be carefully recorded Can the patient get out of bed walk or climb stairs? Can he comb his hair tie his shoelaces unscrew a bottle cap or sweep the floor?

Organs other than the joints which deserve special attention in the physical examination of the arthritic patient include the skin subcutaneous tissue eyes pharynx lymph nodes lungs heart liver spleen muscles and nerves

Valuable clues to the diagnosis of the joint disorder come from abnormalities of the *skin* Associated urticarial wheals point to serum sickness Petechiae and ecchymoses suggest meningococcemia

or a defect of blood coagulation a butterfly rash systemic lupus erythematosus and erythema marginatum rheumatic fever

The patient complaining of arthritis of the hands may exhibit no evidence of arthritis but rather diffuse swelling of the subcutaneous tissue as seen in the early stages of scleroderma *Subcutaneous nodules* are frequently encountered in patients with various forms of arthritis Those occurring on the extensor surfaces of the forearms just distal to the elbows are thought to be the hallmark of rheumatoid arthritis although sarcoid or lupus nodules or gouty tophi may occasionally occur in the same location A striking feature of the nodules of rheumatoid arthritis is their symmetry The nodules in rheumatic fever are more transitory less symmetrical softer and not so frequently near joints the distribution of those of polyarteritis nodosa and amyloidosis tends to be linear along the course of affected arteries The external ears should be carefully searched for gouty tophi Tophi or nodules near joints are usually fixed to the periosteum or the joint capsule Synovial cysts *ganglions* should not be mistaken for nodules or tophi

The ocular examination may yield useful information in differential diagnosis Conjunctivitis may suggest Reiter's syndrome keratitis gonococcal arthritis or Clutton's joints uveitis rheumatoid arthritis or sarcoid cytoid bodies systemic lupus erythematosus and retinal arterial thromboses polyarteritis nodosa

Similar differential diagnostic analyses can be constructed for the other extraarticular organs previously listed

Laboratory Tests After a careful history has been recorded and a thorough physical examination performed the aid of certain appropriate laboratory studies should be obtained The *hematologic examination* should be performed in all arthritic patients In rheumatoid arthritis rheumatic fever or sarcoid anemia may be mild or moderate in some patients with collagen vascular disease it may be more severe In rheumatoid arthritis the anemia is typically hypochromic and normocytic whereas in systemic lupus erythematosus it is usually normochromic and normocytic but may be hemolytic The white blood cell count is usually slightly elevated in serum sickness rheumatic fever many cases of active rheumatoid arthritis and some infectious arthritides it may be greatly elevated in other infections polyarteritis nodosa and leukemia Conversely leukopenia frequently accompanies tuberculous arthritis Felty's syndrome systemic lupus erythematosus and sarcoid In purpuric states the platelets should be counted and when indicated further special studies on blood coagulation performed

The erythrocyte *sedimentation rate* is one of the more important laboratory determinations in rheumatology It is particularly useful in (1) the differential diagnosis of the mild early case (2) estimating the severity of the inflammation in those conditions such as rheumatic fever or rheumatoid arthritis where the rate is known to be elevated and (3) determining by serial tests the course of the arthritis and the effect of therapy Among the disorders of joints the rate is usually high in infectious arthritis serum sickness acute phases of rheumatic fever rheumatoid arthritis and variants and collagen vascular disorders acute gouty arthritis and neoplasms in or near joints Normal values are recorded in degenerative joint disease traumatic arthritis neurogenic arthropathy fibrositis psychogenic rheumatism and between acute attacks of inflammatory or gouty arthritis The test is nonspecific A normal rate cannot be relied upon to rule out such diseases as rheumatic fever or rheumatoid arthritis because the disease may be only minimally active or there may have been technical difficulties In such cases the determination should be repeated Various nonspecific acute *phase reactions such as that to C reactive protein* may also help to estimate the activity of the arthritis

Other *serologic* tests may also aid in diagnosis One or more of the serologic tests for syphilis (STS) may not only indicate that the patient has one of the several rheumatic sequelae of this infection but also augment the physician's alertness to the possibility of gonococcal arthritis If the STS is positive a *Treponema pallidum* immobilization test (TPI) should also be performed since it has been shown that many patients with a false positive STS have some form of connective tissue disease The antistreptolysin O titers of serum help greatly to confirm the diagnosis of rheumatic fever being elevated in more than 85 per cent of patients with active polyarthritis caused by this disease

The sheep cell agglutination test is positive in approximately 75 per cent of patients with active peripheral rheumatoid arthritis unaccompanied by psoriasis or spondylitis and in over 90 per cent of patients with subcutaneous nodules It is not entirely specific for rheumatoid arthritis however and positive tests may be found in patients with systemic lupus erythematosus or progressive systemic sclerosis (scleroderma) Other serologic agglutination tests for brucellosis or tularemia or gonococcal complement fixation are occasionally useful

If possible *L E cell* preparations should also be made in arthritic patients especially those in whom the diagnosis is in doubt The importance of this test is readily grasped when one realizes that arthralgia or arthritis is the presenting manifestation

in one third of patients with systemic lupus erythematosus

Since the rheumatic manifestations of gout are so pleomorphic all patients with joint complaints should have a blood *uric acid* determination

Urinalysis and tests of renal function may help in difficult diagnostic situations by focusing one's attention on the possibilities of Reiter's syndrome gout one of the collagen vascular disorders or amyloidosis secondary to rheumatoid arthritis

X ray findings also aid materially when interpreted in the light of clinical and other laboratory information They should not be considered the final arbiter however since different types of arthritis may produce identical roentgenographic changes Furthermore even in obviously inflamed joints the x ray findings may be totally negative in the early stages of illness

Bacteriologic cytologic and chemical examination of *synovial fluid* may provide further information of diagnostic and prognostic importance The splendid monograph by Ropes and Bauer has done much to increase our knowledge of the characteristics of joint fluid both in normal persons and in those with various pathologic states

Normal synovial fluid is small in volume clear pale yellow sticky and relatively acellular It is essentially a dialysate of blood plasma the albumin passing through readily but the globulin passing through with difficulty The fluid which helps to lubricate the articulating surfaces contains mucin a protein polysaccharide complex similar to that found in the ground substance of connective tissue

A proper examination of joint fluid should include all those features recorded in the analysis of fluid from other body cavities i e volume appearance specific gravity reaction cell counts including a differential and concentrations of protein and sugar (with comparative blood levels) Anaerobic as well as aerobic cultures should be planted immediately A Gram stain of the centrifuged sediment should also be carried out If tuberculosis is suspected an aliquot of the fluid should be inoculated into a guinea pig The turbidity should be estimated and the fluid observed for clot formation The diluting medium for white cell counts should be physiologic saline and not acetic acid because the addition of acetic acid to normal joint fluid so precipitates or denatures the mucin that a ropy clot is formed An icteric index of the joint fluid may be helpful in cases where traumatic arthritis is suspected

Fluids obtained from patients with joint disorders fall into two antagonistic groups and there is a third group with *intermediate findings* Diseases included within the first group are degenerative joint disease traumatic arthritis neurogenic arthropathy osteochondromatosis and osteochondritis dissecans In these disorders the amount of fluid is usually increased but the changes from normal are small slightly more polymorphonuclear leukocytes slightly less mucin and therefore slightly reduced viscosity

The second group comprises all the specific infectious arthritides Reiter's syndrome rheumatoid arthritis and intermittent hydrarthrosis The aspirated fluids in this group appear turbid clot readily and have a low viscosity Although there is considerable variation the white cell count is elevated largely as a result of a polymorphonuclear response Sugar concentration is usually reduced and the protein concentration is elevated with a considerable contribution from the globulin fraction

Among the disorders which fall in the intermediate group the findings in systemic lupus erythematosus hemophilia and hypertrophic osteoarthropathy more closely resemble those in the first group those of the second are more frequently seen in the synovial fluids of rheumatic fever gout and synovial tumors

It is thus clear that in many situations where diagnosis is difficult such as between rheumatoid and gonococcal arthritis the solution may not be found by cytologic or chemical analysis of the synovial fluid On the other hand in many other situations as in the patient who has either a Charcot joint or gonococcal arthritis or others in whom the choice lies between traumatic or rheumatoid arthritis the diagnostic dilemma may be resolved by such an analysis

When all the above methods have failed to clarify the diagnostic problem a *biopsy* specimen of an affected joint may be obtained The value of the histologic method in the diagnosis of rheumatic disease however is somewhat limited by the paucity of accumulated experience not only in diseased joints but in normal ones as well This deficiency exists largely because in this country dissection of joint structures at post mortem examination is illegal unless special permission is obtained and joint biopsies have been performed infrequently In doing the latter procedure strict aseptic precautions should be observed A method of securing a punch biopsy of the synovial membrane of the knee has been introduced but its usefulness is limited as in punch biopsy of the liver by the small amount of tissue for examination This deficiency is significant in light of studies describing in several rheumatic disorders great variability in pathologic change from place to place in the same specimen Nevertheless synovial biopsy can answer various diagnostic problems by differentiating gout from rheumatoid arthritis (by revealing urate crystals) or rheumatoid from tuberculous arthritis (by demonstrating acid fast bacilli) More

over biopsy findings have added to our knowledge of the rheumatic diseases by showing for example that sarcoid or progressive systemic sclerosis (scleroderma) may involve the synovium as well as other more usual sites

RHEUMATOID ARTHRITIS

Definition Rheumatoid arthritis (atrophic arthritis chronic proliferative arthritis chronic infectious arthritis) is a systemic disease of unknown etiology in which symptoms and inflammatory change predominate in articular and related structures The course is extremely variable but tends to be chronic and to result in characteristic deformities There are several variant forms of this disease The relationship between these and the classical variety of peripheral rheumatoid arthritis is not clear hence they will be discussed separately

Epidemiology Accurate statistics relating to the prevalence of rheumatoid arthritis within the population at large or within any group of patients with rheumatic complaints as well as the prevalence of individual findings within the disease are not yet available since it cannot be defined closely or diagnosed with precision A large proportion of patients become incapacitated in one study 58 per cent were unable to carry out their ordinary occupations or duties

This malady is not limited to any *age* group It can begin in children nine months of age and in patients in the ninth decade In the United States the onset of the disease occurs most frequently in *the thirty to thirty nine year old group*

Most studies indicate that the disease occurs three times more commonly in women than in men This does not apply at all age groups for in older patients if more definite criteria such as x ray changes are used neither sex predominates There is no racial predisposition

There seems to be a *familial* tendency in rheumatoid arthritis One study concludes that this is the result not of common environmental factors but rather of a genetically determined susceptibility controlled by an autosomal dominant gene with 50 per cent penetrance

It is well established that rheumatoid arthritis is most prevalent in the Temperate Zones more specifically in areas with cold damp *climates* Many patients point with ironic pride to their ability to prognosticate the weather Although this may well be questioned the coincidence of cold damp weather with aggravation of arthritic symptoms is impressive Well controlled studies of the relationship between arthritic symptoms or objective evidence of arthritis and climatic variable have not been carried out

Pathology Rheumatoid arthritis is recognized pathologically by inflammatory changes more chronic than acute predominating in joint structures with a predilection for certain diarthrodial joints There is virtually no specificity to these changes per se and similar changes are seen in various other tissues of mesenchymal origin It is only by the fairly characteristic distribution of the lesions that the disease is discernible

The histologic changes observed depend on the stage and severity of the disease and on the chance selection of the tissue observed They include the usual changes of chronic inflammation edema proliferation of capillaries and fibroblasts and infiltration at first with round cells and a few polymorphonuclears and later with plasma cells This may progress further to the formation of granulation tissue and to fibrosis Within the granulation tissue one sees islands of fibrinoid change and necrosis

The consequences of these *joint changes* are the thickening of the synovial membrane destruction of cartilage and bone and ankylosis The thickening of the synovium assumes the form of villous hypertrophy and may be so extensive that the joint space widens At this stage lymphoid follicles and foci of fibrinoid change may be seen histologically Later the layer of granulation tissue called *pannus* begins to invade and destroy cartilage presumably by interfering with its proper nutrition The villi of the pannus may interdigitate with corresponding villi on the opposing pannus forming the nidus for fibrous adhesions and ankylosis Ossification may take place in these fibrous adhesions and bony *ankylosis ensues Subchondral granulation may* be so extensive that bony trabeculae may be resorbed Changes similar to those in the synovial membrane described above take place in the joint capsule tendon sheaths and bursae

Subcutaneous nodules are frequently located near tendon sheaths or bursae but may also be found distant from these structures Similar nodules are found in other organs of the body Histologically the nodules consist of clusters of granulation tissue in which foci of fibrinoid material and necrosis are surrounded by palisading (lining up) of inflammatory cells mostly mononuclear cells Whereas an old subcutaneous nodule is an avascular structure with central necrosis the young nodule consists of vascular granulation tissue the small arteries often undergoing active inflammatory change (arteritis)

In addition to atrophy and degeneration of *muscle* fibers which presumably are the consequences of disease nodular lymphocytic infiltrates *may be widely distributed* about blood vessels and between muscle fibers Similar lesions however are seen frequently in several other rheumatic dis

eases and indeed the infiltrate closely resembles the lymphorrhagia of myasthenia gravis

Cardiac lesions occur in different forms Healed pericarditis usually focal is seen in as many as 25 per cent of cases at necropsy Granulomatous lesions morphologically similar to those of the subcutaneous nodule are also found in the myocardium and the aortic and mitral valves Lesions indistinguishable from those of rheumatic heart disease are reported to occur in 19 to 60 per cent of autopsied cases of rheumatoid arthritis Although these percentages are probably excessive the relationship between the two diseases seems to be beyond the realm of chance

An *arteritis* then although not common may be found in synovial membrane subcutaneous nodule muscle heart and other organs It is of special interest because it constitutes a common link with the lesions of rheumatic fever and the collagen disorders (systemic lupus erythematosus progressive systemic sclerosis and polyarteritis nodosa)

Secondary *amyloidosis* commonly complicates rheumatoid arthritis occurring in as many as 20 per cent of severely disabled individuals at post mortem examination

Etiology Both the cause and the pathogenetic pathways of rheumatoid arthritis remain unknown Many hypotheses have been put forth only to be discarded because of a lack of convincing evidence

Exhibiting many of the characteristics of an inflammatory process—fever lymphadenopathy inflamed joints leukocytosis and an elevated sedimentation rate—rheumatoid arthritis was once considered to be almost unequivocally an *infectious* disease A few adherents of the "focus of infection" school persist in having their patients free of teeth tonsils and paranasal sinus mucosa Neither removal of the offending focus nor chemotherapy has altered the course of the disease and most patients do not appear to harbor such foci Attempts to transmit the disease via synovial fluid or by transplanting a rheumatoid nodule have failed

Perhaps the most widely held concept of the etiology of rheumatoid arthritis is that it is a disease of *hypersensitivity* This stems in great measure from the analogy drawn between it and rheumatic fever

Some have described a personality structure peculiar to patients with rheumatoid arthritis Convincing evidence that psychologic aberrations initiate the disease is not available

After Hench revealed the beneficial effects of ACTH and cortisone the inference was drawn by many that patients with rheumatoid arthritis were *adrenocortically deficient* However steroid studies on blood and urine reveal normal or slightly low levels in rheumatoid arthritis as in any other chronic illnesses The coincidence of rheumatoid arthritis and Addison's disease is rare Moreover steroid doses required for the alleviation of symptoms in rheumatoids are much higher than those used for replacement therapy in Addison's disease Most investigators agree that steroid therapy in rheumatoid arthritis is pharmacologic and exerts an anti inflammatory action

So we end where we began cause unknown A variety of noxious stimuli can make the disease worse but which if any of these is important initially? More intensive study of the early acute arthritic whether he turns out to have rheumatoid arthritis or not is sorely needed

Clinical Features The over all clinical picture in rheumatoid disease is highly variable with respect to (1) the number of organ systems involved (2) the severity of the involvement and (3) the course of the disease In some patients the illness may be acute and fulminating with appreciable fever signs of intense joint inflammation and the rapid evolution of severe deformities in others mild deformities may develop insidiously and with little discomfort to the patient

The earliest symptoms are frequently not articular but constitutional namely fatigability anorexia and weight loss At this stage many patients complain of paresthesias or numbness of the hands and feet Others begin to notice evanescent aches and pains in muscles and joints It deserves emphasis that these prodromal constitutional symptoms may antedate the onset of arthritis by several months or years

The great majority of patients seek the help of the physician only after the manifestations of joint inflammation—pain swelling redness heat or deformity—have appeared Although virtually any joint in the body may be involved first the metacarpophalangeal and proximal interphalangeal joints of the hands seem to be the most common sites of initial attack The wrists knees ankles and feet are also frequently involved early in the disease In some elderly patients however the disease may first appear atypically in the shoulders or hips and an erroneous diagnosis of degenerative joint disease is often made Rheumatoid arthritis is characteristically a migratory polyarthritis In the representative case the disease migrates from one joint to another at a moderate speed (in most cases much more slowly than in rheumatic fever) Once affected a joint tends to remain inflamed for weeks months or even years Symmetry of joint involvement is an intriguing common feature Tenosynovitis is occasionally seen in rheumatoid arthritis but suggests more strongly gonococcal arthritis Joint deformities are caused by intrinsic articular disease shortening of tendons and the muscle imbalance which results from involuntary splinting (muscle spasm) about an inflamed joint or from inflamma

tory changes in the muscle as part of the rheumatoid process Deformities usually assume the form of flexion contractures Favorite sites for flexion deformities include the metacarpophalangeals wrists elbows and knees Ulnar deviation is a very common deformity and constitutes one of the hallmarks of rheumatoid arthritis Advancing disease also gives rise to various subluxations and ankylosis

The *skin* especially over the extremities and more so distally is cool pale and clammy Excessive sweating of the palms and soles is characteristic Over the fingers the skin appears taut and shiny and erythema of the hypothenar eminences identical with liver palms is a common finding Fleeting erythematous blotches may be present on other areas Purpuric eruptions over the extremities are infrequent There may be hyperpigmentation especially over the joint surfaces

Subcutaneous nodules are found in 10 to 20 per cent of patients with rheumatoid arthritis They are firm nontender round or ovoid masses varying from 2 mm to 2 cm in diameter The overlying skin slides over them easily and they may or may not be attached to underlying structures They are located usually over pressure points and near bones and joints The most common site is the extensor surface of the forearm just below the elbow In the bedridden patient they may appear over the scapulae or the buttocks In general patients with nodules have active and severe disease Nodules are rare in juvenile rheumatoid arthritis ankylosing spondylitis or psoriatic arthropathy Characteristically the nodules persist for months or years Typical rheumatoid nodules both clinically and histologically have also been found in patients with systemic lupus erythematosus thus casting some doubt on the dictum that the subcutaneous nodule is the hallmark of rheumatoid arthritis Moreover the nodules of many other diseases (gout sarcoid xanthomatosis syphilis etc) may clinically closely resemble those of rheumatoid arthritis

Muscle symptoms—aching tenderness and stiffness—may occur early in rheumatoid arthritis as has been stated and are prominent throughout the course of the disease Morning stiffness and stiffness after inactivity are common complaints Muscular atrophy and weakness may be striking To what extent these changes in muscle are due to direct inflammatory disease disuse or reflex aberrations is not known Attempts to demonstrate electromyographic changes indicative of muscle spasm have failed Increased urinary creatine excretion has been recorded in some bedridden patients with severe muscle wasting

Among the various *ocular lesions* in rheumatoid arthritis perhaps the most common is an anterior nongranulomatous usually bilateral uveitis occurring in approximately 2 per cent of cases Episcleritis and scleritis may also appear either as a nonspecific inflammation or as nodules which are histologically similar to the rheumatoid subcutaneous nodule In rare instances such nodules may perforate the sclera and thus cause extrusion of the uveal tract this condition is called *scleromalacia perforans*

During active phases of the disease the *lymph nodes* may be prominently enlarged In the striking case the patient is often thought to have a lymphomatous disease

Clinical manifestations of *heart* disease probably do not occur more frequently in patients with rheumatoid arthritis than in the general population Such a view contrasts sharply with the high incidence of cardiac lesions—granulomatous and fibrotic—reported in post mortem material

Laboratory Findings A mild or moderate *anemia* may be found in active rheumatoid arthritis It is usually normocytic and slightly hypochromic The anemia does not usually respond to iron therapy and never to folic acid or vitamin B_1 Transfusions are rarely indicated Splenectomy is ineffective

The *white cell* count is within normal limits in 80 per cent of cases A mild leukocytosis is common in early active disease In chronic long standing cases there may be a slight leukopenia

The erythrocyte *sedimentation rate* is almost always elevated during active disease and it is valuable as a rough index of activity Other nonspecific host responses which may be used to estimate disease activity include the presence of C reactive protein hypoalbuminemia hyperglobulinemia with elevations predominantly in the alpha 2 and gamma fractions and positive cephalin cholesterol flocculation

Other *serologic reactions* do not correlate well with disease activity and persist in the face of a spontaneous remission or one induced by adrenocortical steroid therapy These include the sheep cell agglutination tests and the agglutination of group A hemolytic streptococci The latter is technically difficult and thus impractical for routine clinical application The sheep cell test is undergoing widespread intensive investigation It is positive in 75 per cent of patients with active peripheral rheumatoid arthritis and in over 90 per cent of patients with subcutaneous nodules The incidence of positive tests is much lower however in the early stages of the disease when it would be most helpful in differential diagnosis Positive tests are found less frequently in juvenile rheumatoid arthritis ankylosing spondylitis and arthritis with psoriasis The specificity of the test for rheumatoid arthritis has been questioned since positive tests are not uncommonly obtained in patients with systemic lupus erythematosus or progressive systemic sclerosis

Both 17 ketosteroids and 11 oxysteroids in the urine are usually within the normal range but occasionally may be decreased as they are in several other chronic illnesses

Synovial fluid findings discussed previously are usually not specific

Roentgen findings in rheumatoid arthritis are less helpful than is generally realized In the face of obvious active inflammation no roentgen abnormalities may be found even after several months This is because the primary pathology resides in the synovial membrane In most patients however at least one radiologic abnormality usually appears within the first 6 months One sees evidence of soft tissue swelling about the affected joints the result of chronic periarticular inflammation At any stage of the disease and often early there may be osteoporosis which first appears in the areas adjacent to the involved joints and later becomes generalized Generalized osteoporosis is more likely to occur in patients on prolonged bed rest and not undergoing physiotherapy As the disease progresses and the articular cartilage becomes destroyed the joint space becomes narrower still later with fibrous or bony ankylosis it may be obliterated and subluxations may be seen

Diagnosis In the patient who gives a history of prodromal symptoms paresthesias weight loss repeated episodes of acute migratory polyarthritis and who exhibits on examination symmetrical deforming arthritis with flexion contractures ulnar deviation and subcutaneous nodules a diagnosis of rheumatoid arthritis may be readily made However the help of a physician is usually sought at an earlier stage of the disease when the clinical picture may be that of an acute febrile polyarthritis or merely monarticular disease There is no single pathognomonic feature to be sought from the history or physical examination nor is there a specific diagnostic laboratory test

There are many syndromes which may mimic rheumatoid arthritis in its early phases One of these is *rheumatic fever* (p 859) which may be differentiated from rheumatoid arthritis in its acute polyarticular form by the history of an antecedent upper respiratory tract infection an elevated antistreptolysin O titer (although elevations are found in 20 per cent of patients with rheumatoid arthritis) evidence of carditis and the dramatic response of the arthritis to salicylates (although the response is occasionally striking in rheumatoid arthritis) Another is *systemic lupus erythematosus* (p 1700) in which arthritis or arthralgia occurs in 90 per cent of cases at some time during the course appears to be typical rheumatoid with deformities in one fourth of the cases and in one third constitutes the initial manifestation of illness With the passage of time the additional involvement of the skin kidneys pleura lungs peritoneum or central nervous system as well as certain hematologic abnormalities such as leukopenia thrombocytopenia and hemolytic anemia and the demonstration of L E cells lead to the diagnosis of systemic lupus erythematosus An acute attack of *gout may* closely resemble early rheumatoid arthritis but may be ruled out by a normal blood uric acid concentration and more conclusively by a failure to respond promptly to colchicine *Gonococcal arthritis* can be differentiated from rheumatoid disease by the demonstration of the microorganism a favorable response to penicillin and perhaps by the complement fixation test In the patients with proved venereal gonococcal infection but sterile synovial fluid a failure to respond to penicillin and prolonged polyarthritis the syndrome is thought by some to be a distinct disease entity Others think it is rheumatoid arthritis triggered by the gonococcal infection

Degenerative joint disease is distinguished from rheumatoid arthritis by the presence of Heberden s nodes the involvement of the distal rather than the proximal interphalangeal joints the extraordinarily infrequent involvement of the metacarpophalangeal joints and the lack of muscular wasting It is also distinguished by a normal erythrocyte sedimentation rate and no anemia and roentgenographically by the presence of osteophytes and the absence of osteoporosis and ankylosis

In the last analysis one of the chief diagnostic aids in rheumatoid arthritis is the passage of sufficient time to observe the course of the disease

Management The term management" is used to emphasize that there is no known cure for rheumatoid arthritis and that proper care should be comprehensive including various measures in addition to the administration of drugs Efforts are directed toward (1) the proper amounts of rest and exercise (2) the relief of pain (3) combating the rheumatoid process (4) preventing deformities (5) correcting deformities which have developed (6) controlling the complications of the disease (7) maintaining adequate nutrition and (8) rehabilitating the patient Of these the greatest need as yet unfulfilled is for reliable methods of arresting the disease process itself

It is generally agreed that the earlier the therapeutic efforts the more salutary the outcome The patient should develop a degree of optimism and confidence but should under no circumstances expect a rapid cure He should be told that although much can be done to relieve pain and prevent crippling the course of his disease cannot be predicted with precision and medical care may be required over months or even years It is also generally agreed that a variety of unfavorable stimuli such as physical injuries infections or emotionally

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order to attain maximal effectiveness the initial dose should be 200 mg three or four times daily Because of the serious side reactions lower doses 300 to 400 mg daily are now recommended but hematopoietic difficulties have occurred even at this lower dosage In view of the toxicity of phenylbutazone it should not be given until after other less hazardous measures have failed it is contraindicated in patients with a history of allergy peptic ulcer or cardiovascular renal disease If after 7 to 10 days of administration the patient does not improve the drug should be discontinued

Adrenocortical Hormones A full and detailed discussion of adrenocortical steroid therapy in clinical medicine including the various types of steroid hormones dosage route of administration contraindications complications and precautions appears elsewhere (p 596) In 1949 when Hench and his associates first demonstrated the prompt and striking subjective improvement in patients with active rheumatoid arthritis given cortisone or corticotropin there immediately emerged high hopes It was not long however before the limitations and dangers of these agents began to be recognized Considerable disagreement prevails upon such issues as whether or not they should be used at all in rheumatoid arthritis when to administer them which of the many steroids to select in what doses for how long and in conjunction with what other therapeutic measures

After several years of experience with these agents certain general conclusions may be drawn (1) Cortisone which is singled out for purposes of this discussion is a potent nonspecific antiinflammatory agent It does not act in rheumatoid arthritis as replacement therapy in a deficiency state as insulin does in diabetes mellitus (2) In the vast majority of patients with active rheumatoid disease cortisone in adequate dosage can induce rapid suppression of the symptoms and signs as shown by regression of fever joint manifestations size of enlarged lymph nodes scleral nodules and other signs of ocular inflammation and pericarditis Synovial fluid findings may revert to or toward normal (3) On the other hand in the face of clinical improvement anemia may not be completely corrected the erythrocyte sedimentation rate may not be reduced to normal levels the serum protein abnormalities may persist and the sheep cell agglutinating titer remain unaltered None of these tests should in itself serve as a guide to therapy (4) The results of cortisone treatment are better in earlier and milder cases Some beneficial results might well have occurred spontaneously Other variables important in the outcome are dose and duration of cortisone administration other concomitant therapeutic efforts and psychologic factors (5) Some patients fail to improve In many instances this may be attributed to irreversible changes severe contractures or ankylosis which had taken place prior to therapy or to insufficient dosage (6) Subjective and functional improvement usually exceed objective improvement. Joint destruction as shown by serial roentgenographic studies usually progresses (7) Cortisone therapy by itself is insufficient and should be combined with the usual conservative program—rest, physical therapy and salicylates Actually cortisone has proved an exceedingly helpful adjunct to both physical therapy and orthopedic surgical correction

It should be strongly emphasized that cortisone is hazardous and should be withheld until the fullest possible trial with rest, physical therapy and salicylates regularly given has failed to modify the course of the disease Nevertheless the concept that cortisone therapy should be a measure of last resort can be carried too far Time is important in rheumatoid arthritis the patient should not be allowed to become irreversibly incapacitated by his disease before cortisone is tried Rapidly progressing disease intractable pain requiring narcotics for control, and the patient s economic and social situation should also play a role in deciding when to institute steroid therapy

It is not agreed what the starting dose should be Some workers start with rather high doses in order to produce maximal benefits and to be able also to discern as early and clearly as possible whether improvement is being gained thus they are able to decide whether or not this form of therapy is worthwhile Others contend and this is the more common view that in such a chronic disease long term therapy will probably be required hence one should start with a lower safer dose 75 to 100 mg or less cortisone daily Whatever the initial dose after maximal improvement has taken place the dose is gradually reduced in a stepwise manner until significant symptoms and signs reappear at which point the dose may then be maintained for weeks or months Since experience has shown that such a maintenance dose is frequently accompanied by a high incidence of serious side reactions many workers have compromised their therapeutic efforts by being satisfied with that dosage level at which minimal side reactions occur This is called the *suboptimal dose* Usually a compromise is reached at levels ranging from 37.5 to 75 mg cortisone daily

Another problem is when to begin withdrawal of cortisone in the hope that the patient may be entering a remission spontaneously As yet there are no means of predicting such a remission However dose reduction should be carried out periodically at least every 6 months Whenever possible it is wise to resist the temptation of re treatment be-

disturbing situations may incite flare ups in the disease Thus a comprehensive approach to the patient is paramount At each visit the physician must allow sufficient time for a complete inventory of the patient s status

Evaluation of the efficacy of any therapeutic agent or method in rheumatoid arthritis is fraught with difficulties The variable and protracted nature of the disease calls for long term observations before meaningful data are obtained There is insufficient agreement on the criteria of improvement whether subjective objective or functional and the definition of a remission Many studies have been hampered by the lack of precise and uniform methods for measuring objectively the severity of disease activity by poor standardization of cases and by failure to include placebo controls The American Rheumatism Association has set up therapeutic criteria based entirely on objective evidence A functional classification is being more widely used and there is a growing tendency to use various devices for objective measurement in therapeutic trials

For the optimal care of patients with rheumatoid arthritis close cooperation between the internist orthopedic surgeon physiatrist and social worker is essential

Rest and Exercise Most agree that in certain stages of rheumatoid arthritis rest is beneficial In general patients with acute polyarthritis and fever should be at complete bed rest In milder cases 8 to 10 hr at night and brief rest periods during the day should be advised Excessive fatigue should be avoided In order to maintain the patient s morale he should be encouraged to continue work as long as it is not tiring or traumatizing to joints In mild and moderate cases special exercises should be prescribed along with rest to obtain the fullest possible range of joint motion but these should not be so severe that joint pains persist for more than 1 hr thereafter During the periods of severe disease and especially in the early case hospitalization is highly desirable to establish the optimal medical regimen and to institute and instruct the patient in the physiotherapy which he is to continue at home

Relief of Pain Pain relief is important in itself and must be achieved before active physical therapy can be undertaken Many of the physical measures to be described such as the application of heat may help to alleviate pain Drugs such as morphine and Demerol and the like should be strictly avoided because of the danger of addiction Codeine may be used in unusual circumstances for brief periods Since pain is largely the result of inflammation the drug of choice should be anti inflammatory rather than strictly analgesic Three widely used groups of agents help to combat inflammation salicylates phenylbutazone (Butazolidin) or its analogues and adrenocortical steroids in order of increasing potency The choice of one of these agents is conditioned not only by its anti inflammatory activity but also in a very serious way by its relative toxicity

Salicylates should be tried first because they frequently achieve the desired result are least toxic and least costly Acetylsalicylic acid (aspirin) and sodium salicylate seem to be equally effective but care should be taken not to give sodium salicylate to patients with cardiac or renal disease in whom sodium restriction is desired Aspirin should not be given only as needed for pain but regularly and frequently "around the clock in doses to maximal benefit or to tolerance Administration with meals and at bedtime often suffices Gastric disturbances may be overcome by using buffered aspirin or an enteric coated preparation The buffered form may cause distressing constipation The coated tablets sometimes traverse the gastrointestinal tract unaltered

The initial dose of aspirin in ambulatory patients is usually 2 4 Gm daily but if the response is unsatisfactory this should be raised in a stepwise manner until the desired response is achieved or side reactions supervene

Salicylate therapy should be given the fullest possible trial before turning to other agents In those cases not alleviated by salicylates there is considerable disagreement as to whether one should try gold therapy adrenocortical steroid therapy or phenylbutazone A few would give none of these three agents

Phenylbutazone (Butazolidin) has had wide spread clinical trial in various rheumatic states Curiously its effectiveness in rheumatoid spondylitis and acute gouty arthritis seems to be more striking and more predictable than in peripheral rheumatoid arthritis where among various groups major clinical improvement has been reported in approximately 25 per cent of cases The mechanism of its action has not been elucidated although it is said to be anti inflammatory The erythrocyte sedimentation rate does not decrease consistently with its administration Moreover it is potentially dangerous The incidence of side reactions varies considerably In one large series of 800 cases they appeared in 40 per cent of cases and in 15 per cent the drug had to be discontinued A number of fatalities have been attributed to these toxic effects which include serious hematopoietic disturbances such as agranulocytosis hypoplastic or hemolytic anemia and thrombocytopenia peptic ulceration at times with massive bleeding or perforation and retention of sodium and water It is stated that in

ness in the management of rheumatoid arthritis Massage to acutely inflamed joints may be harmful

Occupational therapy is extremely valuable in its own right psychologically and also as a form of exercise particularly of the upper extremities Physiatrists furthermore have developed a wide variety of devices and gadgets such as a long handled comb zippered shoes etc which increase the functional capacity of the crippled patient

Correction of Deformities Although a full discussion of the many methods which have been proposed for correcting joint deformities is beyond the scope of this textbook a few general comments seem worthwhile Stretching exercises usually accomplish little Manipulation of severely involved joints under anesthesia or wedging casts may do more harm than good Various promising surgical procedures for the correction of deformities have been described but need further evaluation

VARIANTS OF RHEUMATOID ARTHRITIS

Juvenile Rheumatoid Arthritis

Commonly called *Still's disease* this disorder begins in children before puberty The earliest reported age of onset is four months Contrary to a generally held view of its rarity a reliable estimate indicates that juveniles comprise 4 per cent of all rheumatoid patients

There are certain differences between the juvenile and adult forms of rheumatoid arthritis Systemic symptoms and signs are more severe in the juvenile Fever often reaches 105 F or higher and may last for months Lymphadenopathy occurs in 60 per cent of cases and splenomegaly in 30 per cent A transient and recurrent rash consisting usually of small erythematous macular or maculopapular lesions is seen in one fourth of cases Larger lesions which occur less frequently are characteristically scaling marginally red and raised and clear centrally Carditis (particularly pericarditis) pleuritis and pneumonitis are common features Subcutaneous nodules are rare The juvenile form tends to affect the larger joints especially in the earlier stages Spondylitis is common The distal interphalangeal joints are more frequently involved than in adult rheumatoid arthritis Impairment of growth and development may take place Leukocytosis is the rule and may be as high as 50 000 per cubic millimeter Sheep cell and similar agglutination reactions are usually negative

Early in the disease differentiation from acute rheumatic fever or systemic lupus erythematosus may be difficult When it presents monarticularly as in the hip or the knee tuberculous arthritis must be carefully ruled out

The natural history of juvenile rheumatoid arthritis has not been fully charted Contrary to earlier beliefs the disease may be mild and result in little deformity Satisfactory functional recovery occurs in three fourths of the patients Also contrary to earlier tenets the disease process does not terminate with puberty In cases with prolonged and severe involvement secondary amyloidosis may appear Management is generally similar to that for adult rheumatoid arthritis Attention should be directed toward the prevention of deformities

Rheumatoid Spondylitis

This disorder (also called *Marie Strumpell arthritis* or *ankylosing spondylitis*) is a chronic arthritis involving the spine sacroiliac joints and in a minority of cases peripheral joints as well Some investigators believe it to be a variant of rheumatoid arthritis and others think it is a separate and distinct but homogeneous disease Still others look on it as a heterogeneous group of diseases with a common symptomatology Those who propose that it is merely a variant point to the pathologic similarities in the two diseases and the fact that involvement of the peripheral joints in spondylitis is clinically indistinguishable from classical rheumatoid arthritis The separatists can marshal several supporting arguments Eighty to 90 per cent of spondylitics are men whereas 60 to 70 per cent of rheumatoids are women Spondylitis usually begins at a younger age Subcutaneous nodules are almost never found in spondylitis When the peripheral joints are involved in spondylitis the common sites are the large central joints—shoulders hips knees in rheumatoid arthritis fingers wrists toes and ankles predominate Serologic reactions such as sheep cell agglutination are usually negative in spondylitis Other perhaps less cogent points include the tendency for spondylitis to produce calcification of ligaments (absent in rheumatoid arthritis) to respond to x ray therapy and to fail to respond to gold Lastly the role of inheritance has been more firmly established in spondylitis It has occurred in identical twins and is apparently inherited through an autosomal dominant gene with a penetrance of 70 per cent for the male and 10 per cent for the female Others notably certain English investigators divide spondylitics into those who respond to x ray therapy and those in whom radiotherapy is ineffective Among the latter they report a high incidence of peripheral rheumatoid arthritis rheumatic fever Reiter's disease and psoriasis

The basic pathologic lesion is a *synovitis* similar to that of peripheral rheumatoid arthritis The disease usually begins in the sacroiliac joints Initially these exhibit condensation of bone later they show punched-out areas articular narrowing and in most instances obliteration of the joint space with bony ankylosis The next event is involvement

cause many exacerbations are temporary (less than 1 month)

The complications of cortisone administration and the contraindications to such therapy are discussed on p 596

Chrysotherapy Until the advent of adrenocortical steroid therapy gold compounds were perhaps the most popular of the specific agents in the treatment of rheumatoid arthritis Their use is highly controversial In spite of more than 9 000 reported cases a critical evaluation of the efficacy of gold in rheumatoid arthritis is almost impossible because of the paucity of well controlled clinical trials Several highly judicious investigators feel strongly that of all forms of therapy for rheumatoid arthritis gold compounds afford the greatest chance of inducing a remission Others believe these agents to be totally ineffective and still others are on the fence

The mechanism of action of gold compounds has not been elucidated They are not effective in any other rheumatic disease Conservative management should be tried before resorting to gold Many patients with sustained disease have entered into a remission coincident with the administration of gold As with other agents the results are usually most impressive in patients during the earlier stages of the disease Significant improvement usually takes place in 40 to 60 per cent of cases among the reported series In several centers conservative management consisting of rest corrective exercises and other physical therapy psychotherapy and salicylates is followed by significant improvement in approximately 50 per cent of cases A few well controlled clinical trials with small numbers of cases indicate little if any advantage for gold and long term studies show no difference in the end results between gold treated patients and those managed by more routine measures Gold is given over several weeks and the reported improvement characteristically occurs gradually The remissions seen after a single course are usually temporary The value of maintenance therapy has not yet been fully determined

Several gold compounds are available most contain approximately 50 per cent of metallic gold and are given intramuscularly The usual regimen consists of an initial test dose of 10 mg a second injection of 25 mg 1 week later and 50 mg weekly thereafter until a total dose of 1 0 Gm has been given Maintenance therapy is usually 50 mg every second or third week

Toxic reactions occur frequently (in up to 40 per cent of cases) vary in severity and are rarely fatal (probably less than 1 per cent) They include skin disorders varying from pruritus to severe exfoliative dermatitis stomatitis hematopoietic disturbances—hypoplastic anemia agranulocytosis or thrombocytopenia—and nephritis With the exception of the hematopoietic damage which may not respond to any form of therapy these toxic reactions usually disappear after gold is discontinued or if severe during treatment with BAL (British anti lewisite) or adrenocortical steroids Prior to each injection the patient should be carefully interviewed and examined for symptoms and signs suggesting gold toxicity There is neither synergism nor antagonism between gold and adrenocortical steroids

Physical Therapy In spite of the emergence of agents which alleviate pain or suppress inflammation physical therapy still remains important in the management of patients with rheumatoid arthritis The overriding principle of such therapy is the maintenance of maximal function by the preservation of normal joint motion and muscle strength

The proper positioning of the patient in bed is essential in preventing postural deformities A bed board should be placed under a firm mattress The pillow under the head should be small in order to combat the tendency towards dorsal kyphosis and flexion contracture of the hips Pillows should not be placed under the knees because they promote flexion contractures

The exercise regimen prescribed for the individual patient depends obviously on the severity of his disease In the severely ill bedridden patient exercises may be confined to passive maximal range of motion at least once daily When the disease becomes less active and joint pain is reduced active exercises may be started These should be done deliberately and slowly and their numbers increased gradually at each of three sessions daily Exercises are best carried out in a warm environment and preferably in a pool Stretching exercises may be helpful if performed conscientiously

Although rest splints are recommended in virtually all the standard writings their value has not been firmly established and their usefulness is limited by practical considerations General opinion is that gutter splints of the legs help to keep knee and ankle deformities to a minimum whereas splints applied to the wrists and fingers may not be successful Patients often complain that such splints are unsightly and burdensome they frequently stop wearing them after a few weeks

Heat locally or generally applied alleviates pain and muscular spasm thus permitting greater range of joint motion Consequently the heat is best administered immediately prior to exercise Locally hot moist compresses may be applied to one or two involved joints usually for 30 min Hot paraffin baths for the hands are especially useful because the heat is retained during exercise Complex devices such as whirlpool baths infrared lamps diathermy or ultrasonics have no special useful

respond to adrenocortical steroid therapy as in typical rheumatoid disease

Felty's Syndrome

In 1924 Felty reported a series of five patients with febrile migratory polyarthritis splenomegaly and leukopenia Subsequently many other such cases have been described and the disease presenting with this triad has since borne his name Three of his five patients also exhibited brown hyperpigmentation over the exposed surfaces Although this disease picture is considered by many to be merely a variant of rheumatoid arthritis it is possible that some of the patients may have rheumatoid arthritis and an unassociated hypersplenism Others may have systemic lupus erythematosus As a distinct clinical entity Felty's syndrome will probably not survive

Arthritis and Ulcerative Colitis

A very small proportion of patients with rheumatoid arthritis develop ulcerative colitis However a much larger proportion (ranging from 4 to 20 per cent) of patients with ulcerative colitis have arthritic symptoms (see p 1461) There are no objective articular signs in more than half of these but in the remainder the changes are those of typical rheumatoid arthritis In most patients the colitis is chronic and severe There is little correlation between the activity of the colitis and that of the arthritis After total colectomy arthritic symptoms may persist This disease must be carefully differentiated from the arthritis complicating cases of bacillary dysentery

Sjogren's Disease

This relatively rare condition of unknown cause otherwise known as *keratoconjunctivitis sicca* comprises dryness of the eyes nose mouth and pharynx in some cases enlargement of the lacrimal and parotid glands (see p 1085) achlorhydria and in approximately 80 per cent of cases joint changes characteristic of rheumatoid arthritis It is found mostly in middle aged and elderly females Interestingly a controlled study has indicated that one third of patients with rheumatoid arthritis have a deficiency of lacrimal secretion Management of the arthritis of Sjogren's disease is the same as that of rheumatoid arthritis

DEGENERATIVE JOINT DISEASE

Definition Degenerative joint disease (DJD) otherwise known as osteoarthritis hypertrophic arthritis or senescent arthritis is a chronic disorder characterized pathologically by degeneration of articular cartilage and hypertrophy of bone clinically by pain which appears with use and subsides with rest and by typical roentgenographic findings It occurs more commonly in older people usually affects the weight bearing joints and curiously the distal interphalangeal joints of the fingers It may develop spontaneously with advancing age (primary osteoarthritis) or at an earlier age as a sequel to articular injury of various kinds (secondary osteoarthritis) The pathologic changes may begin early in life and increase in frequency with each successive decade Pathologic joint changes may not give rise to articular symptoms There are no systemic manifestations as in rheumatoid arthritis

Epidemiology Degenerative joint disease is world wide although it is best known in temperate climates reflecting perhaps the longer life span of the populations in these areas It is an ancient disease In human beings it dates back to Neanderthal man (40 000 B C) It is also known to have afflicted prehistoric animals and changes identical with those in man may be found in a variety of present day animal species

Roentgenographic abnormalities usually do not appear until the third or fourth decade but after the age of fifty virtually everyone has some characteristic x ray changes Nevertheless only a minority experience symptoms Although this disorder is not so disabling as rheumatoid arthritis it has economic importance as revealed by the results of an industrial survey which showed that 14 per cent of all patients exhibiting objective evidence of musculoskeletal disease had degenerative joint disease It is largely a disorder of middle and late life often appearing in women at the time of the menopause Most studies reveal that DJD is divided equally between the sexes although for a variety of reasons (occupational genetic etc) the distribution of joint involvement does differ between them

Etiology Despite the antiquity of this disease only lately have we begun to gain an understanding of its pathogenesis and many questions still remain unanswered It is generally held that DJD is related to the physiologic process of aging Many anatomic studies including the excellent one of Bennett Waine and Bauer in which knee joints from persons one month to ninety years of age were examined reveal that alterations in the articular cartilage characteristic of DJD begin to appear as early as the second decade of life and increase in frequency and severity with advancing age The cause of these degenerative changes is not known Perhaps the most commonly held view is that they result from ordinary "wear and tear" i e from cumulative repeated trauma of various sorts

Although there is little doubt that repeated injury of one form or another frequently plays a role in this disorder this concept does not explain the disease completely A striking exception to this hypothesis is the common involvement of the distal inter

of the spine proper The synovitis is confined to the posterior intervertebral joints since they are the only true diarthrodial joints of the vertebral column Later the spinal ligaments become calcified Demineralization of vertebral bodies presumably on the basis of osteoporosis may appear during any phase of the disease

Spondylitis begins in most cases insidiously with stiffness of the back after inactivity Patients then develop lumbar pain with root radiation often sciatic and some limitation of forward bending Stiffness early in the course of the disease is frequently caused by spasm of the spinal muscles and may be completely alleviated by muscle relaxants such as curare The lumbar spine gradually loses its normal lordosis With progressive involvement of the costovertebral joints chest expansion diminishes and pain may be elicited by deep inspiration coughing or sneezing As the spine fuses it may be held erect the so called poker spine but more frequently the pull of the spinal muscles results in kyphosis scoliosis or both Frequently the head becomes fixed in forward displacement Peripheral joint involvement may either precede or follow spinal disease In many instances it is brief and intermittent but in one fourth of the patients it persists characteristically in the root joints (shoulders and hips)

Although the course of the disease may vary a good deal the usual pattern is persistent activity over the first 2 or 3 years The patients during this period continue to have pain run low grade fever lose weight develop anemia and maintain a high sedimentation rate As the spine fuses pain diminishes and finally disappears on the average 10 years after onset In contrast to patients with rheumatoid arthritis the majority roughly three fourths with spondylitis continue to lead relatively normal lives less than 10 per cent become totally incapacitated Many investigators feel that patients with spondylitis are better motivated than those with peripheral rheumatoid arthritis This however may only reflect the different kind of incapacity produced by the two diseases

The general principles of management are similar to those employed in rheumatoid arthritis—the relief of pain and the preservation of the best possible skeletal function For analgesia salicylates in the fullest tolerable doses should be tried first X ray therapy affords pain relief to many but not all patients It is administered to painful areas of the spine 600 r in air per portal in divided doses The response may be immediate or delayed for 1 or 2 months The courses of therapy may be repeated every 3 to 6 months The customary precautions against spray irradiation should be exercised In spite of the relief of pain by radiotherapy the disease as shown by x ray changes continues to progress Phenylbutazone (Butazolidin) appears to be more effective in spondylitis than in peripheral rheumatoid arthritis It is particularly helpful in minimizing periodic painful attacks in ambulatory patients The contraindications complications and appropriate prophylactic measures as described in the section on peripheral rheumatoid arthritis are equally applicable in spondylitis The indications for adrenocortical steroid therapy are fewer than in rheumatoid arthritis being largely confined to patients with severe sustained disease in whom the peripheral joints are also seriously affected

Special attention should be paid to keeping deformities to a minimum by seeing to it that fusion takes place in the optimal position The bed should be kept flat by placing a board underneath a firm mattress and the head pillow small to prevent kyphosis and neck flexion A small pillow under the lumbar spine may preserve the normal lordotic curvature Exercises of the paravertebral abdominal and respiratory muscles are designed to maintain a straight back and neck and to retain ventilatory sufficiency Muscle relaxants may be useful in the early phases of the disease Back braces may help to combat thoracic kyphosis Rarely in the extremely deformed patient an osteotomy of the lumbar spine may be indicated

Psoriatic Arthritis (or Arthropathy)

Psoriasis occurs in approximately 3 to 8 per cent of patients with rheumatoid arthritis It is generally agreed that the association between these two common diseases is not merely coincidental The psoriasis usually antedates the arthritis by months or years although they may emerge simultaneously or the arthritis may be the first to appear

In most patients the articular lesions are indistinguishable from those of rheumatoid arthritis on clinical roentgenographic and pathologic grounds In a few patients however there is striking involvement of the distal interphalangeal joints with marked articular destruction Frequently this form of arthritis is associated with psoriatic changes of the nails of the corresponding digits The involvement of the distal interphalangeals is the most prominent distinguishing feature and according to some rheumatologists is essential for the diagnosis of true psoriatic arthropathy These joints may be involved alone or in combination with others more characteristic of rheumatoid arthritis Radiologically the changes in the terminal joints may resemble those of gout sarcoid or degenerative joint disease In both groups of psoriatics i e those with classical rheumatoid arthritis and those with arthritis of distal joints subcutaneous nodules are conspicuously absent and serologic reactions are rarely positive

The principles and details of management are similar to those of rheumatoid arthritis The joints

nodules The sheep cell agglutination test is nega tive

Even though x ray changes of an affected joint may be those of DJD the articular symptoms and signs may be caused by a coexistent joint disorder such as rheumatoid arthritis or gout In such cases objective evidence of inflammation may have great diagnostic significance Errors of overdiagnosis are commonly made in cases demonstrating osteophy tosis of the spine this rarely gives rise to symptoms In patients with back symptoms some other process such as a herniated nucleus pulposus and not the DJD may be responsible At any rate if pain believed to be attributable to DJD is severe and fails to respond to the usual measures one must rule out other diseases such as metastasis of a malignancy to bone multiple myeloma or osteo myelitis

Management The most important feature in the care of the patient with degenerative joint disease *is to advise him that although his disease is annoy* ing and at times uncomfortable it is not serious and not the kind (like rheumatoid arthritis) that causes severe pain disability and crippling By such re assurance the patient is spared the anguish of the pronouncement that he has "arthritis and "nothing can be done Conservative measures—adequate rest of the involved joints physical therapy includ ing corrective exercises and safe analgesics such as salicylates—usually suffice Attention should be directed toward eliminating or minimizing second ary traumatic influences Obese patients should lose weight Certain occupational adjustments may be made Abdominal supports for lumbar spine disease aggravated by a sagging abdomen and a Thomas collar or head traction for cervical spine involve ment are other examples of ways to eliminate pre cipitating influences Repeated intraarticular injec tions of hydrocortisone are beneficial only in those patients with a superimposed nonspecific inflam matory response to fragmented cartilage or bone The *systemic use of such potentially hazardous* agents as adrenocortical steroids or phenylbutazone should be discouraged Corrective orthopedic surgi cal methods are useful for severely disabled and painful hips and knees unresponsive to conservative management

HYPERTROPHIC OSTEOARTHROPATHY

Definition This disorder also known as hyper trophic pulmonary osteoarthropathy *osteoarthropa thie hypertrophiante pneumique* secondary hyper trophic osteoarthropathy and Marie Bamberger syndrome is characterized by (1) clubbing of the fingers and toes (2) chronic periostitis with new bone formation at the distal ends of the long bones and (3) arthritis In the vast majority of cases this syndrome is secondary to one of several diverse serious chronic illnesses in other parts of the body in the remainder it is hereditary or idiopathic Be cause of its frequent association with diseases of the lung the disorder is often called "hypertrophic pulmonary osteoarthropathy" but this is a restric tive designation in that the primary disease may reside elsewhere as in the heart liver or gastro-intestinal tract

Formerly chronic suppurative conditions such as bronchiectasis were the most common underly ing diseases but now pulmonary neoplasms head the list Osteoarthropathy may appear several months before the first symptom or sign of broncho genic carcinoma

Classification Hypertrophic osteoarthropathy oc-curs either *symmetrically* all four extremities usually being involved or *unilaterally* affecting only one extremity more commonly an upper Symmetrical disease is subdivided into *acquired hereditary* and *idiopathic forms The acquired form is further* categorized according to the location of the under lying condition

1 *Pulmonary* Various pulmonary pleural and mediastinal disorders lead to this syndrome It occurs in 5 to 10 per cent of cases of bronchogenic carcinoma it has a high incidence in pleural tumors but is rare in tumors which have metastasized to lung Chronic infections include bronchiectasis lung abscess and empyema It is rare in tuberculosis Arthropathy has occurred with Hodgkin s disease aortic aneurysm and other disorders of the medi astinum

2 *Cardiac* Hypertrophic osteoarthropathy oc curs in cyanotic forms of congenital heart disease but is not seen in noncyanotic forms It is sometimes present in subacute bacterial endocarditis

3 *Hepatic* The incidence of this syndrome is high in cholangiolitic biliary cirrhosis but much lower in obstructive biliary portal and postnecrotic cirrhosis

4 *Gastrointestinal* Most of the intraabdominal conditions leading to osteoarthropathy are charac terized by chronic diarrhea They include ulcerative colitis and regional enteritis amebic and bacillary dysentery intestinal tuberculosis polyposis of the colon neoplasms and idiopathic steatorrhea

5 *Miscellaneous* Although it is very rare in spontaneous myxedema (and cretinism) several cases of osteoarthropathy have developed following thyroidectomy for Graves s disease Isolated cases have been described in chronic urinary tract in fections syringomyelia and various other disorders

The *hereditary* form of osteoarthropathy is rare and is distinguished from the acquired form by remarkable thickening of the skin over the face and limbs and by little bone or joint pain It is in herited as a *mendelian dominant* appears shortly

phalangeal joints (Heberden's nodes) These joints are not subject to any more frequent or severe mechanical injury than others such as the metacarpophalangeals which are rarely involved in DJD Necropsy studies have failed to uncover any difference in the incidence of this disorder between laborers and sedentary workers The primary cause does not seem to be vascular in view of the poor correlation between various vascular disorders or more specifically vascular lesions in synovial tissues and the articular changes of DJD

Heredity clearly plays a role in the pathogenesis of Heberden's nodes They are ten times more common in women than in men Stecher showed that they are inherited as a sex influenced characteristic dominant in the female and recessive in the male However the importance of heredity or constitution in the pathogenesis of DJD at other sites has not been demonstrated

Pathology The initial step in the chain of pathologic events in DJD is degeneration of articular hyaline cartilage Grossly the cartilage becomes less elastic yellow and more opaque Under the microscope the surface is made uneven by the appearance of shallow linear furrows which later deepen into clefts or fissures running perpendicular to the surface of the cartilage At this stage the articular surface appears much like velvet on gross examination The cartilage cells form clusters Later there is fraying and then ulceration In this manner the hyaline cartilage is gradually destroyed

In response to this primary injury certain secondary productive or hypertrophic changes ensue In areas where the articular cartilage becomes thin the underlying calcified cartilage becomes thick and dense In the neighboring subchondral bone there is proliferation of fibroblasts endosteal cells and blood vessels This subchondral granulation tissue then breaks through the calcified cartilage to reach the surface of the joint space This surfacing of new bone which later thickens and becomes highly polished is called *eburnation* As a result perhaps of the response to injured cartilage and blood vessel proliferation bony excrescences or osteophytes begin to form at the joint margin These consist of cancellous bone the marrow spaces of which are continuous with those of epiphyseal marrow

Synovial changes occur late and consist of a tissue response to the deposition of debris such as fragments of degenerating cartilage or bone The synovial membrane may appear slightly hypertrophic mostly from fibrosis and with little cellular reaction In advanced cases fibrous thickening and contraction of the joint capsule may be intense Although the mechanism of pain production in this disease is not well understood it is possible that this shrinkage of the joint capsule supplied as it is with somatic and autonomic fibers may be responsible

Clinical Features Only a small proportion of patients with degenerative joint disease have symptoms from the disease Symptoms develop insidiously and consist chiefly of joint pain and stiffness The pain is characteristically aching and mild it appears with exercise of the part and abates with rest The stiffness or articular "jelling" develops after prolonged rest in a fixed position and disappears a few minutes after resuming activity in contrast to that of rheumatoid arthritis which may last for hours Although the disorder is frequently progressive it rarely causes the degree of discomfort and invalidism encountered in rheumatoid arthritis

Objectively the joints may appear entirely normal even in the patient with symptoms Joint enlargement when present is the result of secondary hypertrophy of bone The enlarged joints feel hard and knobby unlike the soft fluctuant swelling in rheumatoid disease There may be tenderness but rarely excessive warmth or erythema In the later stages a grating sensation or crepitus may be felt on moving the affected joint There are no diagnostic laboratory abnormalities or changes in the synovial fluid

In the symptomatic patient the roentgenographic appearance may be normal or exhibit one or more abnormalities These include (roughly in order of advancing disease) unevenness and narrowing of the joint space secondary to destruction of cartilage sharpening of the articular margins irregularity and widening of the articulating surfaces bony sclerosis or eburnation as shown by heightened radiopacity at the ends of bone osteophytes or marginal lipping and bone cysts Osteoporosis does not result from DJD when present other causes should be sought

The most commonly involved joints are those that bear weight (knees hips and lumbar spine) and also the cervical spine shoulders and distal interphalangeal joints of the fingers

Diagnosis Since DJD and rheumatoid arthritis the two most common forms of chronic joint disease in the middle aged and the elderly differ so widely in both prognosis and management it is important to distinguish one disorder from the other In virtually every instance this is readily accomplished Differentiation should never be made on the basis of age alone In contrast to rheumatoid arthritis DJD is confined to the joint structures and is not a widely disseminated systemic disease There are no constitutional symptoms and signs such as fever weakness fatigability anorexia weight loss or muscular wasting nor are there laboratory abnormalities such as anemia leukocytosis elevated sedimentation rate or hyperglobulinemia The joints are not hot or red and there are no subcutaneou

ration In cases where the osteoarthropathy is severe and a satisfactory attack on the primary disorder is not possible relief of disabling symptoms has been obtained by intrathoracic vagotomy or adrenocortical steroid therapy

MISCELLANEOUS ARTHRITIDES

Palindromic Rheumatism

This controversial syndrome of unknown cause consists of recurring afebrile attacks of acute arthritis with pain swelling erythema heat and tenderness The arthritis appears suddenly usually involves a single joint and lasts a few hours or days Attacks are numerous and irregularly spaced during the intervals between them the joints appear normal and function properly Essential to the diagnosis is the absence of residual arthritis even after hundreds of attacks and normal values for the hematocrit and blood uric acid concentration The sedimentation rate may be elevated Some cases demonstrate paraarticular involvement but there are no constitutional symptoms or signs In spite of the fact that many patients diagnosed as having palindromic rheumatism eventually develop typical rheumatoid arthritis or gout the number of patients who seem to fit this description is high enough to warrant continued separate categorization and further study Treatment is symptomatic

Intermittent Hydrarthrosis

This uncommon idiopathic condition consists of joint effusions recurring regularly every 7 to 11 days over several years It is seen mostly in adolescents and young adults Typically it affects the knee (ankle or hip less commonly) and is unilateral The joints in addition to being swollen are often painful and restricted in mobility but not hot or red It is not a systemic disease there is no fever weight loss or muscular wasting there is no anemia and the sedimentation rate is normal Strictly defined it is not a simple hydrarthrosis because biopsy usually reveals a villous synovitis indistinguishable from that of rheumatoid arthritis There is a leukocytosis in the synovial fluid polymorphonuclears predominating Most patients with this diagnosis subsequently prove to have rheumatoid arthritis However 150 cases have been reported with these characteristic periodic effusions over periods as long as 22 years with no residual deformity The disease is refractory to salicylates and physical therapy Some workers believe this condition to be an unusual form of allergy because in a few patients elimination of a food item has coincided with cessation of attacks Antihistaminics are ineffective The response to the intraarticular injection of hydrocortisone is usually favorable Careful exclusion of other rheumatic disorders is essential

Psychogenic Rheumatism

This term refers to the rheumatic manifestations of psychoneurosis in which patients undergoing psychic trauma complain of stiffness pains in joints tendons or muscles and limitation of joint motion In the American Armed Forces during the Second World War psychogenic rheumatism was thought to be the most common rheumatic disease in the British forces such cases were labeled "fibrositis" Essential for this diagnosis are good general health emotional instability lack of joint changes clinically and radiologically normal laboratory findings vacillating complaints and failure to respond to analgesics and physical therapy Some investigators feel that a category of psychogenic rheumatism is unjustified there probably being some organic basis for the symptomatology

NONARTICULAR RHEUMATISM

The patient complaining of "rheumatism" often is referring to symptoms resulting not from joint disease per se but arising from dysfunction of other tissues near joints These include tendons bursae bones muscles nerves and adipose tissue This heterogeneous group of extraarticular disorders is probably responsible for more rheumatic complaints than any one of the various intrinsic joint disorders Approximately 30 per cent of patients who attend arthritis clinics in the United States have nonarticular rheumatism

Fibrositis

This is a controversial unfortunate term which Gowers introduced in 1904 to describe the chronic inflammation of fibrous tissue which he believed to be responsible for lumbago This concept was avidly adopted to explain the various aches and stiffness appearing in various sites of the body and fibrositis has become a wastebasket for many forms of nonarticular rheumatism In addition to stiffness and soreness there are often tenderness and limitation of motion of the affected part The presence of nodules has been overemphasized in many instances these are really fat hernias The frequent sites of pain are the lower back gluteal region neck shoulder and chest Fatigability is the only constitutional manifestation Precipitating factors include various infections such as malaria influenza or pleurodynia trauma environmental experiences such as overexposure to cold dampness or drafts more specific connective tissue disorders such as bursitis or tenosynovitis fat hernias and emotional stresses in a neurotic individual In many

after puberty progresses for about 10 years and remains stationary thereafter

Many cases designated as *idiopathic* are examples of the hereditary form or acquired disease in which the primary condition is unrecognized A few cases of typical osteoarthropathy are however unexplainable

Unilateral clubbing and osteoarthropathy are most commonly caused by aneurysm of the aorta innominate or subclavian Other causes are apical lung cancer axillary tumors subluxation of the shoulder and brachial arteriovenous anastomoses

Pathology The basic lesion is chronic inflammation of periosteum synovial membrane joint capsule and adjacent subcutaneous tissue The periosteum early in the disease exhibits edema and round cell infiltration and at its inner margin osteoid matrix Initially only scattered foci of new bone appear later the distal segments may become completely encased by new bone

The synovial membrane articular capsule and the subcutaneous tissue about the affected bones and joints become thickened and chronically inflamed There may be an intermittent hydrarthrosis Rarely the synovitis goes on to pannus formation ankylosis and degeneration of cartilage

Pathogenesis Theories which have been advanced for the mechanism of osteoarthropathy include (1) chronic infection (2) action of toxins absorbed from the primary focus (3) capillary stasis caused by elevated venous pressure (4) arterial hypoxemia (5) local hypoxia (6) action of local toxins formed as a result of circulatory disturbances (7) anterior pituitary overactivity (8) thyroid underactivity and (9) the elaboration by pleural mesothelial cells of an osteoblast stimulating substance None of these hypotheses accounts for more than a small proportion of cases

The first and only experimental reproduction of this condition was achieved by Mendlowitz and Leslie in the dog by anastomosing the left pulmonary artery to the left auricle thus creating a situation similar to cyanotic congenital heart disease As the osteoarthropathy developed the systemic cardiac output increased (the pulmonary blood flow remaining normal)

After resection of a lung abscess or tumor symptoms and signs of osteoarthropathy frequently subside within a few days The speed of this improvement suggests that the alterations in the peripheral circulation are corrected rapidly perhaps by interrupting an abnormal pulmonary vascular reflex This hypothesis is supported by a recent report of prompt improvement in hypertrophic osteoarthropathy after dividing the vagus in five patients with inoperable lung cancer Thoracotomy alone is ineffective

Manifestations In clubbing the fingertips feel warm and slightly burning but pain is unusual The first change is thickening about the nail bed which can be detected by a reduction in the angle made by the nail and the dorsal plane of the distal phalanx normally about 15 degrees Profuse sweating of the hands and feet is common

Rheumatic complaints vary greatly in severity There may be deep seated burning pain and exquisite tenderness over the distal ends of the bones in acute and advanced cases About the affected bones and joints the skin may be dusky red warm and tender and the subcutaneous tissue thickened The joints may be swollen and their mobility restricted Most commonly involved are the knees ankles wrists elbows and metacarpophalangeal joints There may be slight fever

In the early stages of clubbing the terminal phalanges appear normal on x ray but with advancing disease reveal flaring of the ungual process and osteoporosis The x ray evidence of osteoarthropathy consists of periosteal thickening along the shafts of the long bones appearing first and being thickest in the region of the distal epiphyses especially at the points of musculotendinous insertion The periosteal elevation spreads proximally as the disease progresses Later the cancellous portion of the involved bone becomes osteoporotic and the cortex becomes thin

The course of hypertrophic osteoarthropathy reflects the activity of the underlying disease In cases where it waxes and wanes with exacerbations and remissions of the primary condition the roentgenograms show a tree trunk like layering of thin sheets of newly formed bone In cases secondary to chronic suppuration the osteoarthropathy emerges insidiously and is usually mild In cases secondary to lung tumors the clubbing and arthropathy may appear very suddenly Articular symptoms and signs sometimes antedate clubbing of the fingers but this is unusual

Diagnosis When clubbing arthritic symptoms and periosteal proliferation by x ray are all present this syndrome is easily recognized The patient in whom arthritic symptoms predominate is often thought to have rheumatoid or some other form of polyarthritis In patients with erythema and superficial tenderness especially about the ankles thrombophlebitis is a frequent diagnosis Differentiation from acromegaly is usually not difficult The diagnosis cannot rest on evidence of periosteal proliferation alone because scurvy syphilis trauma lymphangitis varicose veins and other conditions give rise to periosteal disorders

Treatment Therapeutic efforts in hypertrophic osteoarthropathy should be directed toward the elimination of the underlying condition or its amelio

HYPERTROPHIC OSTEOARTHROPATHY

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266 DISEASES AFFECTING THE SKIN

Donald M Pillsbury

The physician possessed of reasonable familiarity with the principles of applied anatomy physiology and chemistry of the skin and with the dozen or so chief patterns of disease which it presents will be able to classify over 90 per cent of all dermatologic syndromes with reasonable accuracy and to treat most of them effectively If in the course of the initial examination the skin lesions of a patient can be classified as representative of a common or uncommon disease as banal or serious as a local disturbance or a manifestation of systemic disease much has been accomplished Many diseases of the skin can be diagnosed with accuracy on inspection providing the examination is adequate and complete as surely as the pathologist recognizes a characteristic cytologic picture Others require further study utilizing all the resources of general medicine and of special laboratory procedures

Dermatologic diseases are encountered rather frequently by the general physician and by all medical specialists On the basis of the enormous United States Armed Forces experience during the Second World War it is clear that any general physician who is practicing in a Temperate Zone will find that some 7 to 15 per cent of his patients present themselves with a chief complaint of a disease affecting the skin In warm humid tropical climates this incidence rises to 25 per cent or more Under conditions of disaster and war the skins of the affected population offer a particularly fertile field for microorganisms and parasites In industry various dermatoses comprise by far the largest group of occupational medical diseases The scope of internal medicine and its subspecialties is so broad and complex as to make it impossible for any physician to be familiar with all of them in any detail In dermatology is in other medical specialties however the most rewarding initial approach is through an understanding of the general principles of anatomy physiology and pathology which have useful clinical application to both diagnosis and treatment

It is essential for the internist to gain an understanding of the characteristics of the principal syndromes which affect the skin In a number of these experience has shown that involvement is almost entirely mucocutaneous and there is no need for extensive procedures of examination other than an adequate general physical evaluation and a few key laboratory studies as in pityriasis rosea certain types of dermatitis acne dermatotropic viral infections (warts molluscum contagiosum) vitiligo most diseases of the hair and nails moderate genetic changes such as mild ichthyosis and benign tumors which may be recognized on clinical examination In most patients these diseases are not particularly disabling and the eventual outcome is ordinarily good Disability and subsequent systemic disease most commonly *result from mistreatment* e g the application of known sensitizing topical agents such as sulfonamides certain antibiotics and antihistaminics the excessive use of ionizing radiation therapy and more and more prominently from the prolonged administration of corticosteroids in doses which are almost certain to produce undesirable physiologic effects

In a second group of diseases affecting only the skin during the initial phase lack of recognition of the nature of the process may be followed by the progression of systemic disease Examples of this group of dermatoses include mild drug reactions the initial manifestations of atopy mild contact dermatitis with continued exposure to the offending allergen bacterial infections which are initially superficial (impetigo and acute folliculitis) but which may produce irreversible systemic infection if not promptly dealt with parasitic infestations such as scabies and pediculosis certain tumors such as active junction type nevi or basal cell and prickle

instances however no cause or precipitating factor is found

Tendinitis and Tenosynovitis

Inflammation of tendons and tendon sheaths may be associated with various types of arthritis or occur independently It is more frequent in gonococcal arthritis (48 per cent of cases in one series) than in any other form of arthritis Occasionally one finds gonococcal tenosynovitis without arthritis Tuberculous tenosynovitis is chronic and destructive The most common site is the wrist Tenosynovitis also occurs in rheumatoid arthritis gout and palindromic rheumatism

Nonspecific tenosynovitis is thought to be a consequence of single or repeated injuries incurred during movements demanding strength and speed The wrist and ankle tendons and sheaths are most commonly involved If conservative therapy (immobilization heat and analgesics) fails local injection of hydrocortisone or surgical excision of the sheath may be helpful

Bursitis

This term is used loosely by patients to signify pain in one or both shoulders To the physician it denotes pain in the region of one of the 140 or more bursae in the body The most commonly affected deep bursae (those situated between bony prominences and muscle or tendon) include the subacromial subgluteal supratrochanteric and Achilles bursae The most frequently involved superficial bursae (those situated between bony prominences and skin) are the olecranon and prepatellar Subacromial bursitis is estimated to be the cause of shoulder pain in 80 per cent of patients who do not have evidence of rheumatic disease elsewhere Its numerous synonyms include subdeltoid bursitis calcific bursitis calcific tendinitis periarthritis of the shoulder and Duplay s disease

The pathogenesis of subacromial bursitis is obscure The generally held concept is that acute or chronic trauma leads to partial rupture of the tendon of one of the short rotator shoulder muscles (supraspinatus infraspinatus teres minor and subscapularis) Calcium is then deposited at the traumatized site Inflammation within and about the bursa is thought to be secondary to the tendinous necrosis and calcification

In acute subacromial bursitis agonizing pain appears suddenly in the region of the shoulder joint and is aggravated by motion especially by abduction of the arm The pain often radiates into the neck or down the lateral aspect of the arm even to the fingertips There is exquisite tenderness over the greater tuberosity of the humerus In approximately half the cases roentgenograms of the shoulder reveal one or more calcific deposits over the greater tuberosity and localized atrophy of adjacent bone The acute attack subsides completely or passes into a chronic phase which is usually mild

Adhesive capsulitis (also called adhesive tendinitis chronic adhesive bursitis or frozen shoulder) is distinguished from subacromial bursitis by a more insidious onset less pain and more stiffness Dense adhesions form between the opposing surfaces of the subacromial bursa Some believe that the initial change is degeneration of the biceps tendon It is thought to result from prolonged immobilization senescent change or trauma In advanced cases the arm becomes locked at the side and the shoulder muscles become atrophic

Therapeutically the acute attack of bursitis may require no more than rest immobilization with slings or splints and analgesic drugs The local injection of procaine or hydrocortisone affords prompt relief in some but not all cases The value of radiotherapy has not been established Aspiration or surgical removal of the calcific deposit is recommended for persistent disabling disease In adhesive capsulitis one may have to resort to manipulation of the shoulder under anesthesia

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Table 135 SKIN UNITS

Cells and layer		*Epidermal appendages*	*Systems*
Keratinocyte, Melanocyte	Epidermis	Hair, Sebaceous gland	Vascular, Neural
Fibrocyte, Histiocyte, Mastocyte	Dermis	Apocrine gland	Extraneous cells
Lipocyte	Subcutaneous	Eccrine sweat gland	Myeloid, Lymphoid

The clinician perceives three fundamental morphologic changes in the skin in *color mass* or *fluid content* The color changes (macules plaques) usually involve the melanocyte or the vascular system Changes in mass (papules nodules tumors) may result from hyperplasia of any of the units listed Growths derived from the keratinocyte *melanocyte and blood vessels are by far the most* common The change in free fluid of the epidermis (vesicle bulla) is fundamentally a reaction of the keratinocyte to injury In the dermis extravascular fluid masks itself clinically as a solid mass (urticaria)

KERATINOCYTE *Keratinization is the most important function of the epidermis* Disturbances or lack of other functions are inconvenient but rarely of crucial importance Complete failure of keratinization is incompatible with life In addition to the hyperkeratinization which results from chronic injury certain genetically influenced changes may be seen an example being congenital hyperkeratosis of the palms and soles Psoriasis is another disease in which there is a disturbance of keratinization with failure of the cycle to be completed In ichthyosis the principal change appears to be a retarded exfoliation of the stratum corneum This may reach severe degrees and be accompanied by atrophy or absence of eccrine and sebaceous glands

An important clinical consideration is that the elasticity of the stratum corneum and the resistance of the skin to chapping are dependent principally upon the water content of the keratin not the oil content Reduction of the water content by low environmental humidity chemical agents or senescence reduces the protective capacity of the horny layer There is no evidence that ordinary ichthyosis is associated with thyroid hypofunction or dysfunction and the administration of thyroid extracts for dryness and ichthyosis of the skin is illogical

MELANOCYTE This is the second important cell of the epidermis In the albino a genetic flaw in enzyme systems (tyrosinase) results in complete failure of pigment formation Negro skin contains an increased amount of melanin but the same number of melanocytes as white skin Local areas in which the melanocyte elaborates too little melanin (vitiligo leukoderma) or too much melanin (chloasma freckles) are frequent

The melanin synthesizing capacity of the skin is regulated by the melanocyte stimulating hormone (MSH) of the anterior pituitary gland There is a balance between this hormone and those elaborated by the adrenal cortex which furnishes an explanation for the pigmentation seen in Addison s disease and perhaps in pregnancy

The melanocyte reacts to injurious stimuli by producing less or more melanin Certain superficial inflammatory processes e g seborrheic dermatitis may produce temporary depigmentation but the ordinary response is increased pigment This is useful in protecting the skin from acute or chronic changes The incidence of epithelioma is directly related to the amount of sunlight to which the skin of the patient is exposed and to a lessened ability to lay down protective melanin in the epidermis With aging the activity of melanocytes varies and dyspigmentation results

Neoplastic change in the melanocyte accounts for the most common of all skin lesions the ordinary pigmented nevus or mole and is the origin of the most malignant of all skin tumors (malignant melanoma) Simple hyperplasia leads to hyperpigmented flat macules (lentigo junction nevus) or even palpable masses Usually brown or black nevi may be flesh colored indicating an absence of function in the hyperplastic cells Not all melanocytic nevi are epidermal Overgrowth of pigmented cells in the dermis gives a blue color (blue nevus mongolian spot)

The interpretation of various types of pigmented lesions in the skin in terms of the possibility of malignant melanoma is a common and vexing clinical problem which is discussed in some detail later

PATHOLOGIC PATTERNS IN THE CORIUM The three principal cells of the corium or dermis are the *histiocyte* the *fibrocyte* and the *mastocyte*

The master cell of the dermis is the fibrocyte the source of collagen and ground substance Normal functioning of this cell is essential to skin repair Unrestrained reparative activity can lead to large deposits of collagen (keloid) This condition is a steady increase in scar tissue which may continue indefinitely in some individuals principally Negroes Benign overgrowth of the fibrocyte produces a simple fibroma Malignant change is rare and produces fibrosarcoma or "spindle cell sarcoma Cortisone prevents the normal development of collagenous tissue and vitamin C deficiency interferes with the elaboration of normal reticulum

The *histiocytes* normally phagocytize particulate matter including melanin (melanophore) lipids (foam cell) hemosiderin some tattoo pigments viruses bacteria fungi and protozoa When confronted with larger masses of material (uric acid crystals petrolatum) histiocytes commonly fuse to

cell epitheliomas in which cure is almost always possible by early treatment and a wide variety of industrial dermatoses hyperpigmentary disorders and photosensitivity reactions

A third group of diseases affecting the skin with which some familiarity is essential includes many conditions which are relatively uncommon but in which an early diagnosis may sometimes lead to complete cure or at least a slower progression of the disease In this group may be included pemphigus syphilis discoid lupus and systemic L E scleroderma miliaria (in which extension of the poral closure may lead to marked disturbances in heat regulation) tuberculosis deep fungous infections sarcoid various purpuras some xanthomas diphtheria cutis many parasitic infestations cutaneous manifestations of lymphomas angiomas acanthosis nigricans psychocutaneous syndromes (especially factitial dermatitis) and chronic effects of physical agents particularly sunlight and cold

In a fourth large group of diseases in which the skin is affected the mucocutaneous manifestations are variable and often incidental though frequently they represent the chief sign through which the nature of the disease may be suspected Examples include the viral exanthems rickettsioses sarcoidosis erythema nodosum leprosy dermatomyositis peripheral vascular diseases erythema multiforme several metabolic diseases neurocutaneous syndromes (adenoma sebaceum) spider angiomas in hepatic disease pruritus as the initial sign of lymphomas or hepatic disease etc

In addition to these there are a considerable number of localized banal conditions in which patients have a consuming interest though they are of no general medical importance A reasonable interpretation of these may often be given not necessarily in terms of any specific syndrome on the basis of the etiologic and physiologic forces involved e g in disturbances of growth or pigmentation of hair and nails Of all the sources of interest and concern of patients about their skin that of possible cancer is paramount and this is constantly increasing as cancer education campaigns and publicity increase An assessment of dermal neoplasms examples of which will be found in every patient examined is a requisite of every general medical evaluation Fortunately the vast majority of tumors and excrescences of the skin are benign and can be recognized as such on close inspection Others must be suspected of being malignant or are patently so In the latter circumstance the sooner the tumor is classified accurately the better

In a short chapter of this type it is not feasible to include detailed descriptions of the wide variety of changes to which the skin is subject This discussion will therefore be confined to a brief summary of the means by which a diagnosis may be established and of certain special laboratory procedures which are not ordinarily used in general medicine A knowledge of diseases of the skin in terms of basic principles obviates much of the need for the use of long and complex designations of individual diseases and their variants

Applied Anatomy and Pathology of the Skin

The skin is a complicated membrane containing a variety of glands nerves vessels lymphatics and muscles It is stratified anatomically in distinct layers epidermis corium (true skin) and subcutaneous tissues

The *epidermis* is about as thick as this paper and highly cellular The *corium* is composed mainly of noncellular collagenous tissue and its energy needs are low It is twenty to thirty times thicker than the epidermis and rests upon the thick *fatty subcutaneous tissue* The *skin appendages* are of two kinds The hair and nails comprise the *keratinized* appendages the apocrine sebaceous and eccrine glands the *glandular* appendages The skin is not uniform In some regions it is adapted to particular purposes and varies in thickness suppleness and looseness The skin of the eyelids for instance is considerably thinner and looser than that of the palms and soles The appendages are characteristically concentrated in certain regions The palms for instance contain eccrine sweat glands but no sebaceous glands the ear lobes contain sebaceous glands but no eccrine glands The reactions of hairy skin differ considerably from those of glabrous skin Intertriginous areas must withstand special stresses The specialized features of the skin in different regions clearly influence the distribution of lesions in certain diseases

The skin serves as an essential anatomic and physiologic shield between the body and its environment Its principal functions are (1) mechanical protection against physical microbiologic and chemical injury (2) perception of a wide variety of noxious stimuli (3) adjustment to environmental temperature (4) prevention of absorption of external substances and loss of body fluids (5) provision of an elastic adaptable covering which permits vigorous movements of underlying structures

Pathologic Patterns in the Skin The fundamental pathologic changes in the skin are few and simple Actually any cellular unit of the skin has but a triad of basic responses to multiple and diverse factors which cause disease These are (1) *functional*—impairment of function in the absence of morphologic changes (2) *inflammatory*—degenerative changes following cellular injury and (3) *proliferative*—increase in the number of cells of given type viz tumors benign or malignant

For purposes of analysis Table 135 presents the units of the skin which may undergo changes

function Its secretion is sterile and odorless but on contamination with the ordinary micrococci of the skin surface it becomes rancid and is the chief source of body odor

The apocrine gland reaches its full development at puberty and disappears with age The chief disease arising from it is *hidradenitis suppurativa* This is not common but may be extraordinarily disabling The sequence of events appears to be in many ways similar to that seen in acne namely a poral closure and blockage with resultant rupture of ducts and extrusion of apocrine secretion into the skin In some individuals infection occurs which may be very difficult to distinguish initially from furuncles If the process is allowed to go unchecked extensive coalescent undermining abscesses form and may be exceedingly persistent The common sites of involvement are the axillas and the anogenital region In some instances cure cannot be obtained until complete excision and grafting of the areas containing the infected apocrine glands are carried out

The *eccrine sweat gland* is an organ of importance in the maintenance of body temperature and is a contributor to a variety of diseases of the skin Man achieves homeostasis in large measure through the action of the sweat glands which flood the skin surface with water to cool it and of the cutaneous blood vessels which dilate or constrict to produce dissipation or conservation of body heat

The master control of the eccrine sweat gland is in the hypothalamus It integrates the effect of thermal sensory impulses which arise in the skin with the blood temperature Either an increase in the skin temperature itself or an increase in blood temperature will result in hypothalamic discharges which relayed through the sympathetic nervous system cause immediate bursts of activity in sweat glands over the entire body There are no inhibitory nerves to the sweat glands Resection of the sympathetic fibers controlling the gland results simply in *anhidrosis*

Sweating may be induced by other than thermal stimuli It may occur on the face as a result of a gustatory stimuli or in association with visceral lesions Sweating may occur as a result of conditioned reflexes i e in anticipation of a warm environment or other stimulus to sweating Emotional sweating is a common experience and has considerable clinical significance in perpetuation of certain types of inflammatory lesions The eccrine sweat gland responds very promptly to both cholinergic and adrenergic drugs Eccrine sweating may be inhibited by atropinelike agents which block the cholinergic stimulus However the clinical usefulness of such therapy is small because no such compound has specific selective effects upon the sweat gland and doses necessary to inhibit sweating produce annoying physiologic effects in other organs

The sweat gland is of no importance as an excretory organ for body wastes though sweat contains small amounts of lactate urea and ammonia and has a level of chloride which may vary from one to two times that of the plasma chloride The chloride level of sweat reflects the circulating level of corticosteroids During the process of acclimatization to heat the level of chloride in sweat drops appreciably Without specific testing of a patient to a standardized heat stimulus it is difficult to be certain of the functional status of his sweat glands

The universal distribution of sweat glands makes it likely that some of them undergo secondary changes of lesser or greater significance in every inflammatory skin lesion Sweat gland involvement may not be perceptible clinically since the gland has no visible surface representation as does the hair follicle and furthermore its secretory function is impossible to assess in the presence of scales exudate and other skin changes Even primary affections of the gland such as miliaria (prickly heat) were for a long time labeled eczema because of the failure to note that the primary change which occurred was in the sweat glands

Anhidrosis may be localized to a single gland or be generalized It may result from a variety of causes including heat stroke surgical trauma to the hypothalamus responses to atropinelike drugs congenital absence of glands and sweat retention syndromes induced by cutaneous diseases It may be a source of unexplained fever tropical asthenia or heat stroke In patients with an anhidrosis of significant degree it may be noted that sweating of the face and neck will be marked but the rest of the skin shows no evidence of sweating

The disturbance of sweating which most clearly results from diseases of the skin is that which results from blockage of the ducts This occurs most frequently as a result of some cutaneous injury For instance blockage of a greater or less number of sweat ducts may be achieved regularly by such stimuli as a mild sunburn a contact dermatitis the application of adhesive tape for 48 hr or the prolonged application of a wet compress If the individual is not stimulated to sweat, either by warm environment or through emotional stimuli no secondary changes in the skin result However if there is a stimulus to sweating sweat may be extruded into the skin rather than on its surface through rupture of the ducts and this promptly results in itching and in a variety of characteristic inflammatory changes which are clinical variants of miliaria If the sweat duct blockage is superficial this is of no importance but if it is deeper the

form multinucleated foreign body giant cells In xanthomas multinucleated histiocytes filled with lipid droplets appear (Touton giant cells) In granulomas the histiocytes change into epithelioid cells which divide into another form of giant cell (Langhans) These are phagocytic and are distinctive of the general group of granulomas of the skin (syphilis tuberculosis leprosy sarcoidosis and deep mycoses)

The third principal type of cell in the corium is the *mast cell* This requires special histologic methods for its demonstration and is rarely seen in routine biopsy specimens The mast cell granules contain both heparin and histamine The mast cells are localized about the vascular system The signal protective role of the mast cell is shown by the fact that it releases its granules in response to any injury with production of immediate vascular changes and an outpouring of leukocytes and plasma from the blood stream This appears to be *the mechanism involved in the production of the triple response* and in dermographism

Overgrowth and aggregations of mast cells produce the condition known as *urticaria pigmentosa* which has been presumed to be a rare disease occurring almost entirely in childhood However this concept is being rapidly extended and the following table indicates the various findings which may be encountered in this condition

Table 136 CLINICAL AND LABORATORY FINDINGS IN THE MORE SERIOUS TYPES OF URTICARIA PIGMENTOSA (MASTOCYTOSIS)

Clinical

HISTORY Months to years with pruritus and dermographism
AGE Over 30 years
SEX Either
SUBJECTIVE SYMPTOMS Nausea vomiting weakness and weight loss
SKIN MORPHOLOGY Macular to nodular red to brown telangectatic
VISCERAL Hepatosplenomegaly

Laboratory

BIOPSY OF SKIN Proliferation of mast cells
BONE CHANGES BY X RAY Generalized osteoporotic osteosclerotic and thickened trabeculae of ribs vertebrae long bones and pelvis when first seen it suggests miliary metastases from carcinoma multiple myeloma or myelofibrosis of depressed bone marrow
STERNAL MARROW Mast cells sometimes present
BONE BIOPSY Nests or sheets of mast cells
SPLEEN OR LIVER BIOPSY Mast cells sometimes present
BLOOD STUDIES Low normal or leukopenic thrombocytopenic and sometimes a monocytosis

SOURCE Nickel W R Urticaria Pigmentosa (Mastocytosis) A M A Arch Dermatol 76 476–498 1957

LIPOCYTE In this the chief cell of subcutaneous fat tissue inflammatory changes are common Nonspecific fat necrosis manifests itself in subcutaneous nodules which may or may not be tender There is often a preceding history of trauma including the injection of various medicinal compounds or reactions to insect bites or thermal injury Occlusive peripheral vascular changes may impair circulation to the subcutaneous tissue sufficiently to result in formation of localized areas of fat necrosis

A *striking specific syndrome which involves* fatty tissue is Weber Christian disease (relapsing febrile nodular nonsuppurative panniculitis see p 1701)

Sebaceous Glands The distribution of these *glands* is distinctive The scalp and face have the greatest number the forehead may contain as many as one thousand glands per square centimeter and it is noteworthy that the glands are largest where they are most numerous Since the gland empties into the terminal hair follicle any condition causin *closure of the follicular ring may lead to retention* of formed sebum This may be followed by cyst formation or if there is rupture of the duct with escape of sebum and of bacteria into the skin moderate to marked chronic inflammatory changes may ensue *Chronic inflammation frequently* produces marked scarring in the skin and is very traumatic psychically in some patients Acneform eruptions may be seen in syndromes such as Cushing s disease and adrenocortical tumors Drug reactions to iodides are commonly acneform though they do not produce the precise sequence of events seen in this disease

Since the follicular unit is peculiarly susceptible to bacterial infection and since such infections may easily become chronic early treatment is desirable particularly in areas where the hair follicles are deep such as the bearded region and scalp It is to be emphasized however that in many instances chronic folliculitis is not due principally to bacteria but is essentially a foreign body reaction

The Sweat Glands Physiologic or anatomic disturbance of the eccrine or apocrine glands produces several distinct skin syndromes and may be a significant contributing factor to the chronicity of eczema and of fungous and bacterial infections

Though the *apocrine gland* is ordinarily referred to as a sweat gland its secretion is entirely different from eccrine sweat Lower Mammalia such as the ape and the dog show many apocrine sweat glands spread over the entire skin surface but in man the gland has become atavistic and regressive The glands are distributed primarily in the ear canal *the axillas the nipples* and the anogenital region though they may occur elsewhere The wax glands of the external auditory canal are modified apocrine glands In man the apocrine gland has little useful

age in relation to diseases of the skin is the increased vulnerability of aged persons to dermatitis ulceration or bacterial infection of the extremities secondary to peripheral vascular disease Destructive effects from all types of physical and chemical trauma are more severe and recovery is slower in older patients

Race Though many diseases affecting the skin occur more frequently in members of particular races this consideration is rarely crucial in diagnosis Pemphigus is more common in Jews but it can occur in Gentiles Kaposi's sarcoma is seen more frequently in patients from southeastern Europe but again this must not be a determining factor Psoriasis is infrequent in pure blooded Negroes but such persons are now rare outside of Africa Pediculosis particularly of the scalp is uncommon in Negroes Negroes also develop bizarre and exuberant cutaneous reactions in secondary syphilis and in sarcoid

Geographic Origin Some diseases affecting the skin can be acquired only under climatic and other conditions which render them contagious and endemic in certain areas For instance a person can almost never acquire leprosy if he has not lived for an extended period in an environment other than a Temperate Zone of Europe or of North America Certain treponemal diseases such as yaws pinta and bejel are seen only in tropical environments indeed bejel is encountered only in the eastern Mediterranean area Contact dermatitis to poison ivy does not occur in England because the plant does not grow there However individuals who are sensitive to poison ivy may have marked reactions to plants of the family Anacardiaceae which have an extensive geographic distribution e g the cashew nutshell mango tree Japanese lacquer tree and dhobie mark tree

While the strong geographic tendencies of some diseases are useful in making a list of diagnostic considerations more complete they may also lead to error If a patient states that he has spent some time in the tropics too great emphasis may be placed on the esoteric with neglect of aggravated forms of common diseases An individual who spends some time in a tropical climate but who is not a native is much more likely to have some very marked form of a disease commonly found in temperate climates such as miliaria or bacterial or fungous infections of the skin than he is to have a disease which is peculiarly and uniquely tropical Moreover it must be kept in mind that the geographic foci of many diseases are expanding and contracting for reasons that are not immediately apparent Coccidioidomycosis is common in the San Joaquin valley of California but there are other areas in the United States in which it is found Creeping eruption due to cat or dog hookworm is very common along the coastal areas of the Southeastern United States but during suitably warm weather with beaches densely populated may extend well into northern New Jersey "Jungle rot" (a thoroughly nondescript term) and "monkey pox" (widespread impetigo arising on miliaria) may be seen among the "natives" of cities such as Philadelphia and Baltimore during prolonged periods of steaming humidity

Seasonal Incidence Certain diseases have seasonal peaks Contact dermatitis will obviously be seen far more frequently during seasons when plants are growing A diffuse dermatitis from airborne or ragweed pollen is invariably first seen in any particular patient during the ragweed season but with recurrence of the disease recovery may be more and more delayed and the seasonal incidence less apparent Photosensitization reactions are at their peak during the summer season often occurring only in areas where there is no filtration of the sun's rays by smoke and other matter but with recurrences the direct relation of the reaction to sunlight may become less evident In all patients with chronic recurrent skin disorders the history of *climatic and other factors at the time of onset* is of great importance Prolonged questioning may be required to elicit this relation in proper perspective and detail

Many diseases including various types of dermatitis and superficial fungous infections become much worse during seasons of high environmental temperature Miliaria is caused almost entirely by this factor and is rare during cold weather Certain common diseases such as acne show variable responses in relation to season Acne is ordinarily improved by exposure to sun but it may become much worse in an environment of great heat and humidity A patient with congenital ichthyosis or senile atrophic skin is often worse during the winter because of the low humidity of artificially heated houses and prolonged exposure of the skin to the pleasure of hot baths Psoriasis and atopic dermatitis are ordinarily much improved during the summer months though not invariably so The very common disease pityriasis rosea shows increased incidence in the spring and fall for reasons which are a complete mystery Erythema multiforme of the recurrent urticarial or bullous types may occur principally during the spring through factors which are likewise unknown

Personal Hygienic and Occupational Factors The skin is subjected to a wider variety of traumatic stimuli than any other organ of the body Through a number of finely adjusted physiologic mechanisms it performs a vital service in the life of the person which it contains It does this with a surprising capacity to maintain its own integrity and functions There are few diseases of the skin in which environ

itching and inflammatory changes and trailing complications resulting from scratching and infection may be very disabling

Special Features of the History in Dermatologic Diagnosis

The *medical history* in a patient with a disease affecting the skin should be obtained with the same care that is exercised in a patient with any general medical or surgical illness However skin lesions are often too quickly assessed as trivial and unimportant their precise extent is undetermined and their general medical importance remains unsuspected

Though it is often useful in any medical history to record the chief complaint exactly as given by the patient this frequently is not the case with dermatologic patients A term such as rash is obviously noninformative and patients often describe their diseases in very colloquial terms Symptoms such as pruritus or pain vary so greatly with skin lesions that often they are not helpful It may be useful therefore to delay putting down the chief complaint until after the initial inspection The initial summary of the complaint should include data on the chief type or types of lesions whether they are localized or diffuse whether the dermatosis is acute or chronic and whether it is associated with symptoms or signs indicative of systemic disease

It is also very useful to record early in the history whether or not any *topical or systemic therapy* has been used and if so what because reactions to such medicaments are very common and frequently greatly obscure the underlying disease It is important to know whether *ultraviolet therapy* has been used whether this produced an exacerbation or improvement and whether any type of *ionizing radiation* or *corticosteroid* therapy has been employed

Otherwise the objectives of medical history in a patient with a disease affecting the skin are precisely the same as those of any other medical history namely to trace the development of the disease as accurately as possible to determine those elements of the patient s past history which may be related to the disease in question and those which are not to establish the relation of the patient and his disease to his heredity personal and occupational environment psychic and emotional status and previous medical care and to establish a good physician patient relationship by an attitude of kindly interest and willingness to listen In many patients who are seen because of a localized process such as a wart or seborrheic keratosis there will understandably be some resistance to extensive questioning and examination However particularly in patients of middle age or above requestioning may reveal that the patient has neglected himself medically and a few simple inquiries regarding the patient s general physical state and emphasis on the value of preventive health examinations may prove highly rewarding The author has had numerous occasions to direct such patients to appropriate general medical care through the small wedge of a banal skin lesion Many patients are curiously enough far more inclined to seek attention for what may be a very minor visible lesion on the skin than for the vague symptoms of more serious conditions

Family History It is obviously of importance in patients with dermatoses which appear to be allergic to inquire concerning allergic manifestations in blood relatives It is necessary that the more common allergic diseases such as hives eczema hay fever and asthma be mentioned specifically Other skin diseases in which a familial trend is frequent include ichthyosis acne baldness rosacea and psoriasis Occasionally skin tumors such as seborrheic keratoses may be strongly familial Less common conditions such as neurofibromatosis epiloia (neurocutaneous syndrome) and encephalotrigeminal angiomatosis may be genetically endowed Disturbances of pigmentation are common in families as is hereditary hemorrhagic telangiectasia (Rendu Osler Weber disease) Benign or juvenile acanthosis nigricans frequently has a high family incidence Many other examples could be cited but most of them are uncommon or rare

Age as a Factor in Diagnosis As with many other diseases certain groups of skin conditions are seen much more frequently in certain age groups Nevertheless great caution should be exercised and age alone should not be allowed to become a determining factor in arriving at a diagnosis This is particularly true of tumors The incidence of cancer of the skin increases with age but it is by no means rare in children (with the exception of malignant melanoma) and is moderately common in young adults Acne reaches its height in adolescence and rosacea in middle age but these conditions are not entirely confined to these age groups Atrophy of the skin and keratoses are characteristic of senility but they occur in young adults who are sensitive to sunlight and even in children (xeroderma pigmentosum) Atopic dermatitis frequently shows an age periodicity and is fortunately not common after late adolescence nevertheless it can persist indefinitely in severe or restricted forms The common types of ringworm of the scalp are seen entirely in children but an adult form has become endemic in the Southwest and Western United States Older individuals are less likely to have severe contact sensitization reactions in the skin and frequently become less troubled by sensitivities such as that to poison ivy Aside from tumors perhaps the single most important consideration of

to tumors as well Considerable confusion exists regarding the term *tumor* which is ordinarily used to designate the larger and deeper circumscribed infiltration of the skin or subcutaneous tissue However it is commonly used to describe lesions which are neoplastic regardless of size or location

The majority of papular eruptions may be diagnosed accurately by clinical examination and appropriate laboratory studies but in those which cannot be classified accurately biopsy is usually mandatory The histologic characteristics are by and large clear cut The most common dermatologic syndromes characterized by papules are tumors psoriasis lichen planus viral infections such as warts and molluscum contagiosum some drug eruptions xanthoma and certain lymphomas though there are many others The initial lesions of smallpox may be papular and secondary syphilis is frequently so The presence of atrophy or frank scarring immediately narrows the diagnostic considerations uncomplicated psoriasis for instance never produces scarring

Wheals (hives) are special types of papules They may remain as small individual lesions but frequently enlarge to form large plaques often with striking geographic outlines or may produce marked swelling of the face or an extremity (angioedema) Acute urticaria is most commonly produced by foods drugs and insect bites The cause of chronic recurrent urticaria is usually difficult to determine psychosomatic influences undoubtedly play a role Wheals are frequently a component of the eruption of erythema multiforme Wheals ordinarily respond to antihistaminics though large doses may be necessary Corticosteroid therapy is usually promptly effective though the lesions recur quickly often in more severe form if such treatment is discontinued without removal of the primary etiologic factor

VESICLES AND BULLAE These are sharply circumscribed collections of free fluid in the skin principally in the outer layers The most common representatives of vesicular dermatoses are contact dermatitis dyshidrosis of the hands and feet and herpes simplex In most instances the principal etiologic factor is readily determinable Bullae which are simply large vesicles represent a very vigorous effort of the skin to counteract some noxious agent Lesions may be bullous in a severe reaction to a contact allergen and of course chemical irritants or physical agents frequently produce a bullous reaction Under such circumstances the cause is ordinarily readily apparent In very extensive or chronic bullous eruptions thorough study is indicated The more important diseases characterized by bullous lesions are pemphigus dermatitis herpetiformis erythema multiforme (Stevens Johnson type) Bullae do not occur in psoriasis in most types of dermatitis other than reactions to contactants or drug eruptions or in acquired syphilis in the adult.

PUSTULES Pustules are simply circumscribed collections of free pus i e very superficial abscesses of the skin Dermatoses showing both vesicles and pustules are very common and vesicles frequently become pustular even in the absence of overt bacterial infection Pustular lesions of the skin cover a very wide range of conditions In pustular eruptions of more than a few days duration pathogenic bacteria are frequently culturable but it must not be assumed from this that all such organisms are necessarily acting as etiologic agents in the eruption

The above are the principal initial lesions of diseases affecting the skin

Other lesions which represent sequential or evolutionary changes are

SCALES These are simply accumulations of loose horny fragments of stratum corneum Certain types of scales are quite characteristic e g the greasy rather yellowish scales of chronic seborrheic dermatitis or the silvery piled up scales of psoriasis The chemical characteristics of scales vary considerably in different processes e g it is possible to make a diagnosis of psoriasis in some instances by simple chemical tests of the scales Such methods have not reached a level which is generally practical but as knowledge of the normal and pathologic biochemistry of the skin increases it should furnish aid in the diagnosis of obscure conditions

CRUSTS (SCABS) These are the dried remains of exudate from oozing erosive or ulcerated skin lesions They may consist of dried blood serum pus or an admixture Unless the diagnosis of a particular dermatosis is readily apparent representative crusts should always be removed to see what lies underneath One of the most characteristic of all crusts is that seen in diphtheria cutis which produces a covering tenacious and adherent unlike that seen in other bacterial infections

ULCERS Since ulcers represent a destructive process of the skin they always require explanation They may vary from small superficial erosions which heal without perceptible scarring to deep sometimes widespread lesions which involve underlying tissues or even adjacent bone If the etiologic factor concerned is not readily apparent such lesions deserve the most thorough study The factors concerned may sometimes be multiple and obscure

SCARS Scars may of course follow ulcers or may result from conditions in which there is no true ulceration e g discoid lupus atrophic lichen planus stasis or circumscribed scleroderma As with ulcers if the cause of the scarring is not apparent thorough and searching study from all standpoints is indicated The differentiation between tempo-

mental factors require no consideration In easily recognizable form they manifest themselves in the calloused hands of the workman the whealing of the skin in a patient with dermographism the characteristic patch of pigmented thickened skin on the neck which marks the violin player the keratoses and skin cancers which may mark the sailor long home from the sea the bullous reactions to trauma occurring in patients with epidermolysis bullosa the fungous infections as a penalty for wearing shoes and the dermatitic reactions to innumerable sensitizing and irritating occupational contactants This list of environmental excitants of cutaneous disease can be extended to include hundreds of examples

Clinical Examination

Inspection of the skin and mucous membranes is the simplest of all the procedures of physical examination Adequate exposure proper illumination good vision and thoroughness are essential Certain sites such as the scalp the folds of the skin the buccal mucous membranes (not just the pharynx) the palms and soles the anogenital region and the vaginal membranes are often not examined Gross diagnostic errors may result solely from insufficient illumination In obsolescent hospital wards and clinic quarters the natural or artificial illumination available is frequently unsatisfactory A flashlight or for that matter almost any small bulb source of illumination is entirely inadequate The physician places himself at a serious disadvantage if he makes a dermatologic examination with light sources which are glaring or produce distorted shadows Natural daylight without glare is the best source of illumination for general inspection of the skin An ordinary stand lamp with at least a 60 watt bulb is also very satisfactory In offices or clinics a wall bracket which permits positioning of the bulb is a necessity if large numbers of examinations are being done Fluorescent lighting is generally unsatisfactory because of flickering and color distortion Certain special surgical type lamps produce a superb shadowless nonglaring illumination of the skin The routine use of a hand lens or a head loop is essential for the adequate interpretation of many small lesions of the skin especially tumors

Diagnosis on the Basis of Presenting Skin Lesions The diagnosis of a disease affecting the skin often depends upon accurate classification of the individual lesions In diseases in which only the skin is involved where there is no systemic disturbance and no specific information obtainable by laboratory studies the morphologic characteristics furnish the only diagnostic clues It is therefore important that they be described accurately This can be done in straightforward simple terms there is no need to use an obsolescent or esoteric terminology The essential facts to be noted are

1 Distribution of the lesions
2 Physical characteristics
   a Flat raised or containing fluid (serous purulent or sanguineous)
   b Size shape and color
   c If palpable any special characteristics

Many conditions of the skin especially chronic ones present a variety of lesions With few exceptions however a skin disease in the individual patient is characterized initially by predominance of a single type of lesion which may be pathognomonic It is the mark of the expert in any field of medicine or surgery that he is able to sort out the presenting signs and symptoms in a complicated disorder and to determine which are representative of the underlying disease This faculty is particularly helpful in classifying diseases of the skin Among the debris of a chronic dermatosis the characteristic primary or initial lesion represents true diagnostic treasure From this it is ordinarily possible to determine the chain of secondary consequential lesions

This section outlines the various types of skin lesions with particular reference to systemic diseases in which they may occur No reference will be made to other parts of the examination but it is not intended to raise the classification of skin lesions to a stature more important than they deserve

MACULE A macule is simply a flat circumscribed *change in the color of the skin* The term ordinarily connotes lesions of relatively small size up to 1 or 2 cm in diameter More extensive changes in color are ordinarily referred to as patches or areas Macular processes are of three general types (1) due to extrinsically derived colored materials such as tattoo marks or imbedded material from lacerations or explosions (2) due to intrinsically derived pigment i e flat moles petechiae and hemorrhages or localized increase or decrease of melanin (3) erythematous reactions to a wide variety of pathogenic agents In the presence of constitutional symptoms or if there are purpuric changes in the lesion macules must be regarded as probable evidence of systemic disease Drug reactions are commonly macular and this possibility must always be considered

PAPULE Papules are circumscribed elevations of the skin varying roughly from a millimeter to a centimeter in size Larger infiltrated areas are often called plaques *Nodules* are circumscribed usually solid lesions which lie deeper in the skin or subcutaneous tissue The term is frequently applied to inflammatory processes e g erythema nodosum or subcutaneous fat necrosis but it may be applied

to tumors as well Considerable confusion exists regarding the term *tumor* which is ordinarily used to designate the larger and deeper circumscribed infiltration of the skin or subcutaneous tissue However it is commonly used to describe lesions which are neoplastic regardless of size or location

The majority of papular eruptions may be diagnosed accurately by clinical examination and appropriate laboratory studies but in those which cannot be classified accurately, biopsy is usually mandatory The histologic characteristics are by and large clear cut The most common dermatologic syndromes characterized by papules are tumors psoriasis lichen planus viral infections such as warts and moluscum contagiosum some drug eruptions xanthoma and certain lymphomas though there are many others The initial lesions of smallpox may be papular and secondary syphilis is frequently so The presence of atrophy or frank scarring immediately narrows the diagnostic considerations uncomplicated psoriasis for instance never produces scarring

Wheals (hives) are special types of papules They may remain as small individual lesions but frequently enlarge to form large plaques often with striking geographic outlines or may produce marked swelling of the face or an extremity (angioedema) Acute urticaria is most commonly produced by foods drugs and insect bites The cause of chronic recurrent urticaria is usually difficult to determine psychosomatic influences undoubtedly play a role Wheals are frequently a component of the *eruption of erythema multiforme* Wheals ordinarily respond to antihistaminics though large doses may be necessary Corticosteroid therapy is usually promptly effective though the lesions recur quickly often in more severe form if such treatment is discontinued without removal of the primary etiologic factor

VESICLES AND BULLAE These are sharply circumscribed collections of free fluid in the skin principally in the outer layers The most common representatives of vesicular dermatoses are contact dermatitis dyshidrosis of the hands and feet and herpes simplex In most instances the principal etiologic factor is readily determinable Bullae which are simply large vesicles represent a very vigorous effort of the skin to counteract some noxious agent Lesions may be bullous in a severe reaction to a contact allergen and of course chemical irritants or physical agents frequently produce a bullous reaction Under such circumstances the cause is ordinarily readily apparent In very extensive or chronic bullous eruptions thorough study is indicated The more important diseases characterized by bullous lesions are pemphigus dermatitis herpetiformis erythema multiforme (Stevens Johnson type) Bullae do not occur in psoriasis in most types of dermatitis other than reactions to contactants or drug eruptions or in acquired syphilis in the adult

PUSTULES Pustules are simply circumscribed collections of free pus i e very superficial abscesses of the skin Dermatoses showing both vesicles and pustules are very common and vesicles frequently become pustular even in the absence of overt bacterial infection Pustular lesions of the skin cover a very wide range of conditions In pustular eruptions of more than a few days duration pathogenic bacteria are frequently culturable but it must not be assumed from this that all such organisms are necessarily acting as etiologic agents in the eruption

The above are the principal initial lesions of diseases affecting the skin

Other lesions which represent sequential or evolutionary changes are

SCALES These are simply accumulations of loose horny fragments of stratum corneum Certain types of scales are quite characteristic e g the greasy rather yellowish scales of chronic seborrheic dermatitis or the silvery piled up scales of psoriasis The chemical characteristics of scales vary considerably in different processes e g it is possible to make a diagnosis of psoriasis in some instances by simple chemical tests of the scales Such methods have not reached a level which is generally practical but as knowledge of the normal and pathologic biochemistry of the skin increases it should furnish aid in the diagnosis of obscure conditions

CRUSTS (SCABS) *These are the dried remains of* exudate from oozing erosive or ulcerated skin lesions They may consist of dried blood serum pus or an admixture Unless the diagnosis of a particular dermatosis is readily apparent representative crusts should always be removed to see what lies underneath One of the most characteristic of all crusts is that seen in diphtheria cutis which produces a covering tenacious and adherent unlike that seen in other bacterial infections

ULCERS Since ulcers represent a destructive process of the skin they always require explanation They may vary from small superficial erosions which heal without perceptible scarring to deep sometimes widespread lesions which involve underlying tissues or even adjacent bone If the etiologic factor concerned is not readily apparent such lesions deserve the most thorough *study The factors con*cerned may sometimes be multiple and obscure

SCARS Scars may of course follow ulcers or may result from conditions in which there is no true ulceration e g discoid lupus atrophic lichen planus stasis or circumscribed scleroderma As with ulcers if the cause of the scarring is not apparent thorough and searching study from all standpoints is indicated The differentiation between tempo-

rarily hypertrophic scars and keloids is sometimes difficult to make temporary hypertrophy and elevation of scars after injury is by no means uncommon and may persist for several months Scars are frequently slightly painful or itchy Scars from ionizing irradiation are particularly vulnerable to trauma of all types especially sunlight Extensive scars from whatever cause but most particularly thermal burns tuberculosis and x ray therapy are prone to malignant changes

Configuration of Lesions Three characteristics of the configuration or arrangement of multiple lesions have considerable usefulness They are

GROUPING Characteristic grouped aggregations of vesicles occur in herpes simplex zoster and dermatitis herpetiformis Id reactions in the skin to infections are sometimes grouped i e in tuberculids or dermatophytids The multicentric foci of epithelioma (*in situ* type) are frequently grouped and gradually coalesce to form a single tumor plaque

ANNULARITY This is a striking feature of many dermatoses and reactions to systemic disease Pityriasis rosea lichen planus superficial ringworm infections bacterial infections urticaria erythema multiforme sarcoidosis discoid lupus syphilis deep fungous infections and other processes may produce rather characteristic annular lesions

LINEARITY A linear arrangement of individual lesions may come about as part of the basic pattern of the disease as in localized scleroderma linear nevi and even herpes zoster In some diseases the skin reacts to trauma in a characteristic linear pattern as in lichen planus and psoriasis Scars and keloids are frequently linear Viral infections such as warts may be inoculated in the skin by a scratch

THE PRIMARY INOCULATION OR CHANCRE COMPLEX The association of a lesion at the site of inoculation with regional adenopathy or with a more or less linear development of subsequent lesions is most commonly seen in acute bacterial infections (see p 907) Syphilis produces the best known of all the chancre complexes but this reaction is now observed rarely Primary inoculations of tuberculosis and certain deep fungous infections such as blastomycosis sporotrichosis and coccidioidomycosis may follow a pattern of development of an inflammatory papule and ulcer at the site of inoculation Regional adenopathy and the later development of inflammatory lesions along the areas of lymphatic drainage may occur The recognition of such a mode of reaction is important in the case of tuberculosis or the deep fungous infections as distinguished from spread of the lesions to the skin from a visceral focus because the resistance displayed to the infection after inoculation in the skin is often very high and such infections are usually self limited

Distribution Patterns of Skin Lesions In some diseases the pattern of distribution of skin lesions over the body is so characteristic as to be almost pathognomonic in others while one distribution pattern may be most characteristic variations from it are frequent The following are diseases which tend to involve certain sites

ACNE Since acne is a disease in which the follicular orifices and sebaceous glands are affected the lesions are concentrated in areas where these structures are most abundant large and active The face is the most frequently involved site but lesions appear on the shoulders chest upper back neck and upper arms in more extensive forms of the disease The lack of involvement of the scalp is striking even in the most severe cases only the scalp margins are invaded An even more extensive distribution may be seen in so called tropical acne in which the entire trunk may be affected with lesions on the buttocks and thighs as well

ROSACEA The lesions of rosacea occur in a highly characteristic pattern In severe and long standing examples diffuse involvement of the face may be noted but the flush areas are the sites affected initially These are the malar prominences the nose the forehead and point of the chin Rosacea is often seen in middle aged persons who have had acne in adolescence There is frequently an associated seborrheic dermatitis In the more severe forms pustules are common but these do not characteristically derive from blackheads as does acne The differentiation of rosacea from discoid lupus or systemic L E is ordinarily easily made though of course the two conditions may coexist The eyes should always be examined in rosacea however mild because of the infrequent but severe complication of rosacea keratitis

SEBORRHEIC DERMATITIS This is a third member of the common triad with acne and rosacea In seborrheic dermatitis of moderate severity the scalp may be the only site involved but the following areas are affected in approximate order of frequency in more extensive cases eyebrows skin above the bridge of the nose sides of the nose ears (especially the external auditory canals and retroauricular region) presternal and interscapular areas eyelid margins (a frequent source of chronic blepharitis) intertriginous areas on any part of the body especially the axillas the anogenital region and under the breasts in women The skin of the involved areas is peculiarly susceptible to acute or chronic secondary bacterial infection the intertriginous areas of the toes are rarely involved

PSORIASIS A tendency to involve the scalp knees elbows and back is characteristic of at least 75 per cent of all cases of psoriasis The most common alternate distribution of psoriasis is to the seborrheic areas Psoriasis is frequently misdiagnosed because

of a failure to examine the skin carefully and to determine the presence of lesions elsewhere This is likely if there is involvement of the nails (which is common in psoriasis) in which the condition may be wrongly diagnosed as a fungous infection if there is involvement of the feet and hands there may be confusion with ringworm infections and with syphilis if there is involvement of the genitalia it may be taken for moniliasis

PITYRIASIS ROSEA The individual lesion of pityriasis rosea is annular and ovoid often with a slight border and a characteristic narrow band of moderate scaling just inside this border In the efflorescence which follows the appearance of the primary or mother plaque the lesions tend to involve principally the trunk and upper portions of the extremities with the long axis of the lesions strikingly arranged along the lines of cleavage Even in examples of the disease in which the lesions themselves are unusual namely urticarial or more inflammatory this distribution pattern still holds The most common alternate distribution is a tendency for the lesions to occur distally on the extremities with relative absence of involvement of the trunk Pityriasis rosea may involve the neck but rarely the face It is a banal disease though sometimes very worrisome to the patient The course is that of a low grade infection though a causative organism has never been found Second attacks occur in no more than one per cent of patients Treatment is usually not necessary but if the lesions are extensive inflammatory and pruritic corticosteroid therapy for 3 to 4 days will usually give prompt relief

SCABIES The female *Acarus* prefers the following sites for her burrows the interdigital spaces of the fingers the palms the flexor surface of the wrists the axillary folds along the belt line the buttocks the genitalia in men and about the areola of the breasts in women The head is almost never involved in adults

ATOPIC DERMATITIS (DISSEMINATED NEURODERMATITIS) The objective changes in this very chronic disease are principally the result of rubbing and excoriation they involve the face neck antecubital spaces popliteal fossae wrists and thighs The condition commonly disappears after age twenty five but sometimes persists in a more localized form such as a chronic dermatitis of the hands

CONTACT DERMATITIS Reaction of the skin to external agents which includes primary chemical irritant effects and true sensitization reactions has a characteristic distribution involving the exposed sites in the case of industrial contactants plants and air borne pollens and chemicals

LICHEN PLANUS This chronic and pruritic disease is of little systemic significance The milder forms involve the buccal surfaces of the cheek the genitalia the flexor surfaces of the wrists and the trunk In the hypertrophic form the most marked lesions may be found on the lower legs this is the usual location of the lichen planus like lesions of Atabrine dermatitis

There are of course many other diseases with more or less characteristic patterns of distribution

Laboratory Methods of Dermatologic Diagnosis

The laboratory aids used in general medicine are helpful in arriving at a diagnosis of a disease affecting the skin Several special methods are useful

Biopsy Biopsy is an essential procedure in almost all chronic dermatoses in all pigmented lesions which are excised and in all lesions where there is a possibility of malignant change or serious systemic disease The diagnosis of some lesions will require the services of a pathologist with special training in dermatopathology Others present a clear cut pathognomonic picture and are easily diagnosed by the general pathologist A process involving the skin is seldom static The skin is not bathed in a homeostatic milieu as are internal organs it is subjected to numerous external influences which may disguise the primary process It is the responsibility of the clinician to exercise care and judgment in the selection of the lesion to be examined in determining which technique shall be used in obtaining the biopsy and in providing an informative protocol The specimen should be typical of the process and least subject to secondary trauma Generally this is the most recently evolved lesion Occasionally more than one biopsy may be required before the exact nature of a disease can be determined Multiple biopsies may be needed in large lesions such as chronic ulcers evolving at the site of an old burn or in granuloma inguinale

While consideration should be given to the cosmetic results in the procedure it must be emphasized that an inadequate biopsy specimen benefits neither the pathologist the physician nor the patient The most satisfactory procedure is removal of small lesions *in toto* (excision biopsy) and with larger lesions the removal of an elliptic specimen with its long axis through and at right angles to the border of the lesion In selected instances a 2 mm punch may provide adequate information and leave only a small inconsequential scar (see Fig 204) A 5 mm biopsy punch is sometimes required Bleeding may be stopped by pressure and the application of a small disk of gel foam or by electrodesiccation The scar from this procedure is small and tends to contract and become more linear in the course of time

The Tzanck Test Cytologic examination of the roof of a fresh bulla is useful in determining whether or not the process is pemphigus The

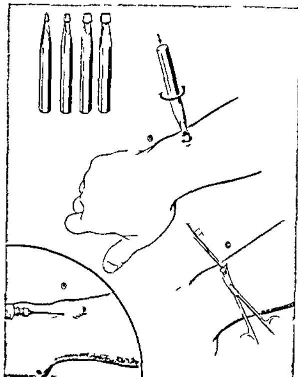


FIG 204 Punch biopsy This is a useful method for obtaining tissue from lesions in which complete excision is not feasible or when multiple biopsies may be desirable The removal should extend to the subcutaneous fat Punches of various diameters 2 to 8 mm are shown (*Pillsbury D M W B Shelley and A M Kligman "Dermatology* p 1331 *Philadelphia W B Saunders Company* 1956)

youngest vesicular lesion present is swabbed with an alcohol sponge the vesicle roof split with a scalpel and the fluid sponged away with dry gauze After the walls of the vesicle are reflected the base of the lesion is scraped gently with a scalpel to remove the basal epidermal cells The whitish material is smeared onto a clean glass slide dried in air fixed in methyl alcohol and stained with a routine Giemsa stain It can be mounted in balsam or examined directly after application of immersion oil to clear the cells In pemphigus one sees numerous small round epithelial cells many in isolated form No prickle cells are seen and there is a basic acantholysis The nucleus is large in relation to the cytoplasm which may be condensed in a basophilic peripheral ring

The Evaluation of Pigmented Nevi

It may be stated at the outset that it is impossible to examine any single pigmented nevus and state positively that it will *never* undergo a malignant change On the other hand it is neither feasible nor justifiable to undertake wholesale excision of pigmented moles some degree of clinical judgment must be exercised

Pigmented nevi are often not manifest at birth but characteristically develop during infancy and childhood and a few do not appear until adulthood Nevi first appear as macules These lesions are ordinarily of two histologic types (1) those in which the skin appears normal histologically except for increased deposition of melanin and a greater number of melanocytes at the *epidermal dermal junction* and (2) lesions which show clumps or aggregations of nevus cells apparently "dropping off or being extruded from the epidermal dermal junction into the underlying corium The first type is known as an *inactive junction nevus* the second may be active or inactive As the child becomes older these macules may become thickened and slightly elevated and the histologic picture changes with cords or bands of nevus cells becoming aggregated in the corium This lesion is called a compound nevus *part epidermal and part dermal* With the further passage of time more elevation of the lesion occurs and the nevus cells aggregate *entirely within the corium* This is the intradermal nevus a mature lesion which is almost always benign

In children a pigmented nevus can evolve rapidly with cellular features of hyperplasia and anaplasia resembling a malignant melanoma of the adult To this lesion the term *juvenile melanoma* has been applied However true malignant melanomas are so rare in childhood that it is often justifiable to delay decision about removal of a suspicious nevus until puberty

The presence of pigment alone does not indicate that a papule or tumor of the skin is a melanocytic nevus Certain entirely unrelated tumors many of them benign may show marked hyperpigmentation The seborrheic keratosis or wart a very common lesion is the best example of this Histiocytoma a common fibromatous lesion arising from the corium (seen on the lower legs of women) may also be pigmented Senile or actinic keratoses are sometimes dark and *pigmentation is frequent in* basal cell epitheliomas (see Fig 205)

Flat Lesions These are simply macular pigmented spots On histologic examination they show junctional activity in over two thirds of instances In such lesions *even pigmentation* and *sharp definition* of the border are reassuring In adults a very high proportion of such lesions will prove to be lentigines and of little significance in regard to potential malignancy However *if the pigmentation becomes speckled and the border more hazy and irregular* the odds are in favor of junctional activity and the lesion must be regarded with suspicion

Slightly Elevated Lesions Such moles are intermediate *between flat pigmented and those* which are raised above the surface of surrounding skin The lesion is clearly palpable Most will prove to be compound nevi and will give some evidence

of junctional activity Many of them particularly in younger patients will evolve in time into "pure" intradermal nevi They need not be excised routinely

Nevi with Pigmented Halo These are ordinarily slightly elevated lesions the base of which is surrounded by a flat pigmented ring with a border that is sometimes irregular These lesions are very likely to show junctional activity and should be adequately excised

Verrucoid Lesions Pigmented nevi with a markedly verrucose surface are raised and often very dark Some three fourths of such lesions show histologic evidence of junctional activity while the rest are intradermal

Raised nevi take other forms these include lesions with a polyploid or raspberry like surface a dome-shaped flat lesion a lesion attached to the skin by a thick pedicle and lesions definitely papillomatous sometimes attached only by a thin stalk These four types of lesions tend to be of the intradermal type and need not be excised unless definite changes are noted in them

Certain general considerations in the assessment of nevi apply to all morphologic types A *sudden change in the pigmentation* either to more marked pigmentation to splotchy irregular character or to fuzziness at the border of the lesion must be regarded with suspicion particularly in flat lesions However it must be kept in mind that melanocytic nevi show variations in pigment at puberty and during pregnancy and to some degree after exposure to sunlight

The presence of fully developed stiff hairs in the nevus is a reassuring sign While it is not an absolute dictum that hairy moles do not precede melanocarcinoma it can be said that they rarely do Such lesions are often frequently traumatized by repeated pulling of the hair or during shaving We have never observed an instance of melanoma arising from such a lesion though there are isolated reports of this

Changes in Size *A significant change in size* of a pigmented nevus in adults must almost always be regarded as a basis for excision The one exception to this is the common occurrence of acute or chronic follicular infection in hairy nevi with the development of tenderness and swelling Such inflammatory changes are no cause for alarm but if the mole becomes repeatedly infected excision is advisable

Ulceration and/or bleeding of previously quiescent moles are two signs of melanocarcinoma which are most commonly mentioned in cancer propaganda However these are late changes and it is essential to recognize the more subtle prodromal changes in moles if melanocarcinoma is to be controlled

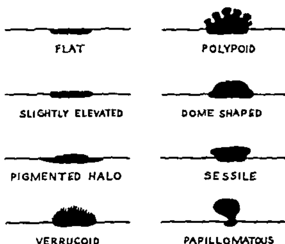


FIG 205 Various morphologic patterns in pigmented nevi The lesions in the left column are in general more likely to be junction nevi. (*After Shaffer B A.M.A Arch Dermatol* 72 120–132 1955)

Pigmented Lesions of the Mucous Membranes Melanocytic nevi may involve the stratified epithelium of the mouth and mucocutaneous junction of the anus Such lesions are usually flat and may be exceedingly difficult to interpret clinically The decision is often crucial because melanocarcinoma arising in the mucous membranes is rarely cured Pigmentation of the mouth in Negroes is common and is ordinarily blotchy and fairly diffuse Hyperpigmentation from chronic irritation e g along the bite margin is also common and need not be a cause for worry In the Peutz Jeghers syndrome pigmented macules of the mouth lips and/or digits may be associated with intestinal polyposis The most difficult lesions to interpret are freckles on the lips or dilated superficial blood vessels usually veins which are commonly blue black and may become sclerosed While these latter lesions are usually recognizable punch biopsy may occasionally be indicated

Special Cutaneous Disease Problems

Acne This is the classic stigma of adolescence almost a normal physiologic reaction in the skin The various clinical manifestations of acne have been designated by a variety of terms Most of these have little meaning or usefulness to non specialists but it is convenient to grade the severity of acne from I to IV as a guide in selecting the types of therapy which are most likely to be helpful Hereditary determinants condition the follicular orifice target organ" response yet fundamentally the excitant is hormonal At least 75 per cent of both sexes show some evidence of acne at the age of puberty There is no significant sex difference in incidence or severity

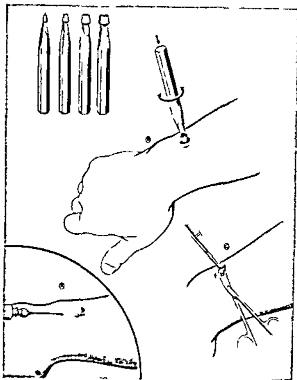


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inadequacies of previous treatment In so called tropical acne a very widespread and severe pustular eruption may develop on the face and entire trunk usually in persons who have had some evidence of acne previously but not infrequently in those in whom there has been no previous sign of the disease Treatment is futile until the patient can be placed in a cool dry environment

X RAY THERAPY The opinion expressed here on x ray therapy for acne is at variance with almost every textbook of dermatology or radiotherapy with which the author is familiar It is the author's belief that the value of such treatment has been greatly overrated but this is a controversial matter The author does not administer x ray therapy for acne

Acne was one of the first diseases of the skin for which x ray therapy was used Its popularity was based upon a supposed specific selective effect on the sebaceous glands The rather limited and surprisingly few controlled studies which have been done on the therapeutic effects of x ray therapy in acne have failed to demonstrate any immediate good effects with doses which may be regarded as comparatively safe in so far as late effects on the skin are concerned In these studies varying amounts of ionizing irradiation in divided doses have been administered to one side of the face while the other side was left untreated No difference in the progress of the acne of the two sides has been demonstrated

ACNE SCARRING The treatment of acne scars has long been considered unsatisfactory but the technique known as skin planing or surgical planing or dermabrasion is useful The most popular method involves freezing the skin with an ethyl chloride or Freon refrigerant spray followed by mechanical removal of the epidermis and upper dermis by means of a high speed rotary steel brush The epidermis then regenerates rapidly from the numerous pilosebaceous and sweat gland units which remain The rotating wire brush has almost completely replaced the sandpapering method formerly in vogue both because the technique is simpler and because of the occasional development of small foreign body granulomas from imbedded silicate granules after sandpapering

Superficial Fungous Infections (Ringworm)

The resident cutaneous flora is predominantly bacterial but a single fungous genus *Pityrosporum* with two species is also represented *P ovale* a yeastlike budding organism occurs in abundance in the scalp and in areas of high sebaceous gland activity but its etiologic relationship to dandruff or seborrheic dermatitis has never been proved *P orbiculare* while normally a skin resident may play a part in the development of the common banal disease tinea versicolor Saprophytic mold fungi are numerous in the atmosphere and spores contaminate the cutaneous surface more or less continuously For the most part they remain dormant on the skin but are problems in mycologic diagnostic work because of their tendency to overgrow culture plates Common weed fungi such as species of *Penicillium* and *Aspergillus* proliferate on diseased skin and have often been wrongly incriminated as the primary cause of cutaneous disease Weed fungi are particularly prone to colonize necrotic ulcers the inflamed ear canal and disease of the subungual skin but recovery of these fungi from such areas should not be interpreted as signifying pathogenicity

The importance of the superficial fungi as a cause of many cutaneous diseases has been considerably exaggerated and has led to many unnecessary reactions from treatment by irritating so called "fungicidal compounds" It is worthy of emphasis that inflammatory reactions on the feet are by no means always due to fungi and even if the pathogenic fungus is recovered this may be only a minor contributor to the inflammatory changes which may be present

The superficial ringworm infections may be divided into two main groups (1) the keratinolytic and (2) the nonkeratinolytic a miscellaneous group The distinctive property of the ringworm fungi is the possession of an enzyme which enables them to digest keratin With this biochemical equipment the nails can be disintegrated hair dissolved and the scaffolding of the stratum corneum the keratinized cells demolished The matrix of the hair and nails is not attacked nor the epidermis itself Except in unusual instances there is no tendency whatever for these fungi to invade living tissue nor has any toxin been isolated However sensitization to ringworm fungi may be induced This is seen most strikingly in inflammatory reactions occurring during the course of ringworm of the scalp or in some instances of acute inflammatory eruptions of the feet

The ringworm fungi or dermatophytes are divided among three genera *Trichophyton Microsporum* and *Epidermophyton* At least one pathogenic ringworm organism (*M gypseum*) has been repeatedly isolated from the soil which it presumably inhabits as a saprophyte By and large however human infections are contracted either from infected animals or from other human beings Certain species the so-called *anthropophilic organisms* show a distinct preference for human beings occurring rarely or not at all in animals The best example of this is the organism which commonly causes ringworm of the scalp especially in urban areas *M audouini* The *zoophilic ringworm* fungi

In some patients comedones may begin to develop at the age of nine or ten and if these patients are from a family stock in which acne has appeared frequently the outlook is disquieting The evidence of acne may persist for a variable period of time probably never less than a year but sometimes spanning the entire teens with extension well into the twenties The precise hormonal excitation of acne is not understood in complete detail ACTH injections in *susceptible individuals* of any age may produce acne Eunuchs do not develop the disease

The treatment of acne is not always satisfactory Although the hormonal stimulus is basic to the development of the disease there are no regularly effective means of combating it from this etiologic standpoint The routine administration of estrogenic hormones is illogical though there are selected cases in which a striking menstrual periodicity of the eruption seems to make such treatment advisable The therapeutic attack on acne must be on the fringes (1) local therapy which may help in relieving the plugging and rupture of the follicular orifice (2) control of contributing factors such as food or drugs (3) judicious drainage of purulent lesions by means which are least likely to produce scarring (4) combating infection with appropriate antibacterial measures and (5) taking advantage of natural aids such as sunlight as fully as possible None of these measures is curative in the strict sense all are palliative and serve only to keep the acne in check and to prevent undue scarring until the hormonal and sometimes emotional storm of adolescence has subsided

The treatments used for acne are extraordinarily numerous In assessing the value of some of them no particular attention seems to be paid to the associated factor of the passage of time in judging the true curative influence of a particular method There are some methods moreover such as stringent restrictions of diet the prolonged administration of antibacterial preparations and the use of x ray therapy which may have bad effects if employed overzealously and without good medical judgment

Preparations containing sulfur and resorcin are undoubtedly useful in mild acne particularly if the lesions are superficial They should be used to the point of producing a mild chapping effect Regular removal of comedones is helpful in some patients and with proper instruction may be done safely at home Drainage of frankly pustular lesions requires judgment It should not be done too early in the course of the lesion but may promote more rapid healing if performed when the nodule is fully fluctuant and the infection near the surface

The restriction of foods and drugs is important in many patients with acne but should not be done on any routine basis It can be shown without question that iodides bromides and Tridione make acne worse Foods such as chocolate nuts and coffee so frequently cause exacerbations as to make routine elimination justifiable From this point on it is advisable to individualize dietary elimination It should be kept in mind that in most patients with acne juvenile growth is rapid and energy output high so that dietary restrictions should be advised with care and good reason

Trauma to the skin may induce and perpetuate inflammatory acne lesions Constant pinching rubbing and picking of the face may become a subconscious habit and lead to much scarring because the acne lesions are not given a chance to heal spontaneously Violent traumatic exercise such as wrestling or football sometimes produces inflammatory acne lesions as does the rubbing of sweaters dirty sweat shirts or bacteria laden shoulder pads and other gear

In chronic severe acne in which there is unmistakable evidence of bacterial infection antibacterial therapy is often effective and justified As is the case with many chronic bacterial infections of the skin particularly if there is a tendency to formation of minute to larger abscesses within the skin such therapy must often be continued for long periods of time and should be initiated and supervised with good medical judgment Though penicillin is useful at times the incidence of acquired or potential allergic sensitivity to it is high Sulfonamide therapy is sometimes adequate but it may be necessary to employ broad spectrum antibiotics In general the drug should be given in full dosage initially to determine whether or not it will be effective following which the dose may be reduced to the lowest level which appears to keep the infection under control

Hormonal therapy of many types has been used in acne usually with indifferent results The routine administration of thyroid extract has long been a favorite treatment but the author is not convinced of its effectiveness Mention has been made of the occasional use of estrogenic hormones both topically and systemically Though such therapy may sometimes appear to be helpful it should be used on the basis of adequate endocrinologic study and supervision More recently the administration of corticosteroids systemically has enjoyed a considerable vogue In the author s experience there can be no question whatever that the anti inflammatory effect of such treatment on acne lesions may be marked sometimes with very small doses but the inherent physiologic risks of such therapy must be very carefully weighed against the fact that acne is a purely local disease with no systemic manifestations

Sunlight and vacation have a good effect in acne and may provide a striking demonstration of the

extend over the dorsum of the foot If the dorsal surface of the toes is involved a contact dermatitis from applied medication or from footgear should be suspected

During exacerbations of the vesicular type of ringworm infection the lesions frequently fuse and contain a yellowish gelatinous fluid Fungi are often not demonstrable at this phase because they are being cast off so rapidly Vesicles on the sole may be so deep as to appear papular and may not rupture spontaneously

The most chronic type of ringworm infection of the feet is caused by *T rubrum* This is frequently unilateral It is characterized by diffuse scaling often of a fine branny character by relative lack of inflammation and by extreme chronicity The process may become diffuse over the entire plantar surface and extend over the sides of the foot in a moccasin distribution The condition is sometimes difficult to differentiate from ichthyosis from a congenital keratosis or from psoriasis

Involvement of the toenails is almost inevitable in any long standing fungous infection of the feet This may be difficult to differentiate from the traumatic distortion which occurs inevitably in the toe nails of older persons particularly men Fungi are hard to isolate in scrapings taken from the nails because they are overshadowed by keratinous debris bacteria and molds It is probable that fungi in and under the nails are the chief source of what appear to be reinfections of other parts of the foot

TREATMENT Any experienced clinician who has seen many cases of ringworm of the feet must come to the conclusion that treatment frequently does more harm than good In particular it should be kept in mind that though hundreds of chemicals have antifungous effects in vitro no chemical which will be tolerated by the living skin is capable of killing fungi in hair nails or thick pieces of stratum corneum It is obviously unphysiologic to use compounds which are primary chemical irritants or which have sensitizing capacities The most effective methods of treatment are simple They include

1 *Dryness* This is the most important single factor especially in intertriginous involvement A patient with subacute or chronic ringworm should be most meticulous and careful about drying the toes after bathing It is helpful to do this with a dry crash washcloth with friction sufficient to remove scales and macerated skin The wearing of tight occlusive footgear should be avoided whenever possible and during warm weather the wearing of sandal type or aerated shoes is worthwhile If there is excessive perspiration the use of a nonabrasive foot powder is helpful it may be found advisable to change the socks once or twice daily Socks of an absorbent variety are best though they should not be too heavy during warm weather An elaborate ritual of boiling socks has no demonstrable value the sources of reinfection are numerous enough on the foot itself

2 *Rest* is helpful in the treatment of inflammation of the feet due to fungi In severe exacerbations bed rest may be essential In less severe forms the patient should restrict walking and athletic activity

The actual treatment of the infection is dependent upon the degree of inflammation In acute bullous exacerbations foot soaks of any bland solution either hot or cold are helpful Vesicles and bullae should be opened this may be done safely by the patient himself with a needle or with curved manicure scissors Tops of bullae should not be cut away completely because this exposes the underlying epidermis A shake lotion may be used sparingly to advantage and in this phase hydrocortisone in a lotion is often helpful Ointments should be used only after the process becomes less acute and should be applied at night rather than in the morning It is of particular importance that evidence of secondary bacterial infection be watched for For very severe acute attacks a short course of systemic corticosteroid therapy may be justified

In subacute or chronic types of fungous infection whether intertriginous vesicular or dry scaling type several preparations are useful The fatty acids are helpful and rarely cause irritation Castellani s paint is especially good for intertriginous areas and for patches of vesicles If there is thickened skin on the soles or macerated debris between the toes a preparation which will increase exfoliation should be prescribed Care must be taken however that it is not applied in a concentration which will produce damage Between the toes a preparation containing 3 per cent salicylic acid and 6 per cent benzoic acid in 70 per cent propyl alcohol is useful The same chemicals may be incorporated in an ointment type base yielding a half strength Whitfield ointment Some patients may find fatty acid ointments more helpful An alternate type of preparation is one containing salicylic acid and sulfur usually in a concentration of 2 or 3 per cent each *It is reemphasized that the treatment of superficial fungous infections of the skin is unsatisfactory in terms of a specific antifungous agent and that treatment should be directed toward making the conditions for the growth of the fungi less optimal toward allowing the skin to recover as rapidly as possible during acute exacerbations and toward assisting the skin to cast off the fungi which are present entirely in the stratum corneum or in the nails*

It has been suggested though on debatable evidence that the presence of a ringworm infection of the feet particularly that caused by *T rubrum*

on the other hand are frequent pathogens of domestic animals from which they may be transmitted to human beings The anthropophilic species have the clinical peculiarity of causing relatively noninflammatory and often very persistent types of ringworm while the zoophilic organisms tend to incite short lived inflammatory diseases in man

The transmissibility of ringworm infections has been greatly overrated It can be demonstrated regularly only in certain types of ringworm infections of the scalp occurring almost entirely in children In adults the transmission of the common types of ringworm infections of the feet groin and nails remains to a great extent a mystery It is difficult to produce an infection with superficial ringworm fungi experimentally in man regardless of the conditions of exposure It is a curious fact that ordinary ringworm infections of the feet though common in young men are relatively uncommon to rare in children in adult females and in the aged Familial infections with superficial ringworm fungi with the exception of tinea capitis are very uncommon This is in contrast to some other infections such as the virus of warts in which infection of all members of the family living together is sometimes observed

An important principle that provides much insight into certain peculiarities of the host parasite relationship in ringworm infections is that if superficial ringworm infections become markedly inflammatory there is a tendency toward spontaneous cure Marked inflammation is incompatible with the continued proliferation of the fungus because it is either desquamated along with other products in the wake of the inflammatory reaction or finds itself in an inhospitable environment owing to interference with normal keratin synthesis The success of the ringworm parasite in entrenching itself on the surface is dependent on its *not* provoking much reaction in the host This is particularly well seen in one of the most chronic of all common ringworm infections of adults that due to *Trichophyton rubrum* in which the inflammatory changes may be minimal but in which the infection once established may persist for many years On the other hand when the parasite injures the host to the point of provoking a significant tissue reaction it seals its own doom and the infection is almost always short lived This type of spontaneous cure is the basis for a clinical rule that such lesions should be treated conservatively Antifungous agents become superfluous and unnecessary the treatment is essentially that which might be applied to an acute or chronic dermatitic process of any type

In an inflammatory change affecting the skin in which a diagnosis of superficial ringworm is suspected there are three essential considerations

1 *Is a fungus present?* This may be determined easily by obtaining an adequate scraping from an active portion of the lesion and examination of the scales in a potassium hydroxide preparation Precise cultural identification of the fungus present is by no means always necessary to intelligent treatment though it is of value if the facilities for this are readily available

2 *Is the process acute subacute or chronic?* In the presence of an acute reaction the inflammatory changes will ordinarily subside spontaneously provided chemical or physical trauma to the affected skin is avoided In subacute or chronic ringworm infections nothing can be accomplished in terms of a compound which is specifically fungicidal in vivo there are no such compounds available The therapeutic attack must be by way of making conditions less favorable for the proliferation of the fungi by combating inflammation by assisting the exfoliation of infected skin and by preventing secondary bacterial invasion

3 *Are factors other than fungi contributing to the inflammatory changes seen?* Examples include excessive sweating and maceration primary irritations or sensitizations from applied medication and physical trauma from shoes or clothing

Ringworm of the Feet This is the most common type of ringworm infection and is largely a penalty for wearing shoes The majority of young American adult males acquire fungous infections of the feet the incidence being between 40 and 80 per cent The rate is highest in semitropical to tropical climates Fungous infections of the feet are extremely rare in children and are not common in adult females

The favorite sites of involvement in ringworm of the feet are the interdigital spaces especially the third and fourth the inner side of the arch, and the toenails Scaling is a constant feature of subacute or chronic fungous infections of the feet Inflammation in interdigital spaces may be variously caused by fungi by *Monilia* by simple maceration or may be due to psoriasis or some other disease of the skin If inflamed fissures are present secondary bacterial infection may be suspected The fungus most commonly cultured is *Trichophyton mentagrophytes* The intertriginous involvement may remain chronic and localized or may sometimes show acute exacerbations with the formation of vesicles and bullae extensively over the feet and with vesicular lesions elsewhere on the body particularly the hands ("id" reaction)

Ringworm infections of the feet may persist as occasional patches of vesicles which tend to localize on the instep portion of the sole and on the heel and ball of the foot In severe cases the entire sole may be involved The process does not commonly

duce the lesion called a *kerion* This has the appearance of a bacterial infection and in time involutes spontaneously with cure of the ringworm infection usually without permanent alopecia In ringworm of the scalp acquired by children from animals in which *M canis* is the most common causative organism the process is ordinarily inflammatory from the onset and is self limited

Ringworm of the scalp in children is a considerable public health problem and the incidence of the infection rises and falls in urban centers for reasons which are not readily apparent Treatment with antifungous agents is unavailing in terms of cure of the infection Involution occurs only if the infected hair shafts are cast off either as a result of inflammation developing around the hair follicles or through exposure to x rays in an amount which will produce temporary epilation Though the latter procedure in the hands of experts is reasonably safe it admittedly represents a rather drastic form of therapy It becomes essential in some instances however but the indications for the procedure should be very carefully considered

Various fungi are capable of producing chronic infection of the scalp in adults Favus caused by *T schoenleini* is relatively common in eastern Europe but is rare in the United States Another type of adult ringworm of the scalp that due to *T tonsurans* has long been seen with considerable frequency in Mexico and is being encountered increasingly in the Southwest United States and in California The condition resembles seborrheic dermatitis or psoriasis and there is usually moderate to marked loss of hair It cannot be detected easily because there is no fluorescence on Wood s light examination as is the case with almost all ringworm infections in childhood The proper diagnosis is made in most cases only if the clinical acuity of the examiner is high and if adequate mycologic studies are done

Pemphigus

Pemphigus is an uncommon relapsing disease which affects the mucocutaneous surface initially There are no signs of systemic disease at the onset but these soon develop secondarily Pemphigus is invariably fatal within a few months or years if adequate treatment is not instituted The disease is ordinarily controllable with corticoid therapy

The most common type of pemphigus (pemphigus vulgaris) is characterized by tense or flaccid bullae of varying size They appear without symptoms as a rule on skin or mucous membranes which had seemed entirely normal Occasional slight itching or burning may be noted The bullae rupture quite readily especially in the mouth pharynx and vagina leaving denuded areas These erosions or superficial ulcers are very slow to heal and often enlarge gradually When healing occurs no scarring results if there has not been secondary infection In some patients particularly those with brunet skins there may be marked residual hyperpigmentation

The distribution of lesions in pemphigus is variable though areas which are subject to rubbing pressure or stretching are more prone to develop lesions In pemphigus the epidermis readily detaches upon lateral tension and this phenomenon (Nikolsky s sign) may be demonstrated by drawing the finger over the surface of the skin with firm pressure The epidermis slides off much like a piece of wet tissue paper Though this sign is almost always present in pemphigus it may be seen in other bullous diseases as well e g epidermolysis bullosa and widespread bullous drug eruptions

The lesions of pemphigus usually involve the mucous membranes as well as the skin In many patients the initial lesions are entirely oral and/or vaginal The disease attacks adults of any age It is not seen in children and is rare during adolescence Members of the Jewish race are most commonly afflicted There is no sex predisposition

Secondary bacterial infection of the bullae or of denuded skin occurs commonly producing the rather characteristic mousy odor of the disease and frequently gives rise to septicemia which is a characteristic complication

Certain variations from the most common morphologic type of pemphigus occur

Pemphigus Foliaceus This is a rare member of the pemphigus group in which the lesions are predominantly those of exfoliative dermatitis Because of the very extensive cutaneous involvement signs of systemic disease may develop rapidly The disease begins with the appearance of small vesicles in which scaling and crusting develop producing a flaky surface similar to that seen in exfoliative dermatitis This is in contrast to the characteristic raw denuded areas seen in pemphigus vulgaris Slow symmetric spread of the lesions occurs and within a period of months the entire body may be covered with exfoliative lesions The hair and nails commonly are lost The histologic picture is characteristic The odor in exfoliative pemphigus is offensive The response of this form of pemphigus to corticosteroid therapy is less favorable than in common pemphigus

In *pemphigus vegetans* many of the bullous lesions are succeeded by hypertrophic vegetative masses in intertriginous areas such as the axillas groin and inframammary region These may later become dry and verrucose The vegetative lesions do not occur on the mucous membranes with the exception of the vermilion border of the lip and sometimes on the vulvar labia The lesions are malodorous and evidence of secondary bacterial infection is always present The process may sug

may induce peripheral vascular disease in the feet and lower legs The author is not convinced that this is true but in any event a ringworm infection of the feet becomes of increased importance in patients with peripheral vascular disease or with diabetes The scrupulousness of foot hygiene must be redoubled and particular care should be taken *not to use chemicals with possible cauterant effects* on the skin because a very slowly healing ulcer may result The services of a competent chiropodist are helpful to such patients not only from the standpoint of maintaining good foot hygiene but in an effort to remove irritation from toenails calluses and footgear

Majocchi's granuloma is a distinctive manifestation of ringworm infection in the form of a granulomatous folliculitis and perifolliculitis It occurs most frequently in women who shave their legs and who have a diffuse *T rubrum* infection of the feet Indefinite and rather indistinct scaling patches develop on the lower half of the lower leg and inflammatory nodules develop at the borders of these patches The nodules rarely exceed a centimeter in diameter and are flat or only slightly elevated If the lesion is observed early it may be seen to be centered by a hair The nodules are not pruritic and usually only slightly tender They do not progress to suppuration and persist as long as 3 or 4 months They may then become slowly absorbed or undergo necrosis and heal with a depressed scar Histopathologic examination reveals a characteristic foreign body granuloma degenerating fungous elements may be demonstrated by the Hotchkiss McManus method

Certain other puzzling conditions of the lower extremities are seen in association with fungous infections of the feet though the precise relation is difficult to establish One is an erysipelas like process of the lower extremities occurring in the form of a recurrent superficial cellulitis of brief duration and apparently representing an id reaction On the legs and elsewhere the following reaction patterns may be in some cases representative of an allergic sensitivity to ringworm (1) erythema nodosum (2) erythema multiforme (rare) and (3) indefinite macular rashes

Ringworm of the Nails When a superficial ringworm infection involves the toenails and/or fingernails topical therapy becomes quite useless Cure may sometimes be effected by removal of the nail plate and careful scraping away of all debris in the lateral gutters and in the nail base However this procedure is rarely successful in the toenails and is not advised Reinfection is usually prompt In fingernails successful cure of the ringworm infection by surgical avulsion is more frequent though probably less than 50 per cent It is more likely to be helpful if only one or two fingernails are involved and if there is not an extensive focus of ringworm infection on the skin of the hand Care must be taken not to confuse other nail dystrophies with a ringworm infection The most common of these are psoriasis chronic dermatitis of the distal phalanges chronic paronychial infection and arthritis involving the distal joint

Ringworm of the Groin This is a common affliction especially in males during the summer months The characteristic lesions are seen in the crural folds and the upper inner thigh usually with an annular scaling ring in the latter area Several other conditions may be confused particularly psoriasis and seborrheic dermatitis Anal and vulvar pruritus are not per se commonly due to fungi though *Candida* may sometimes play a role In tinea cruris it is particularly important not to use compounds which will produce any reaction because the male genitalia are very susceptible to irritation and a chronic dermatitis which is protracted by scratching may result

Ringworm of the Body Extensive ringworm infections of the trunk or extremities are uncommon in temperate climates though they are seen with some frequency in the tropics In the presence of a ring shaped moderately inflamed lesion the odds are generally in favor of some condition other than a *fungous infection e g pityriasis rosea seborrheic* dermatitis or psoriasis In those instances in which a proved extensive fungous infection of the skin of the trunk and extremities is observed in patients in temperate climates patients should be subjected to careful study for hematologic disease or diabetes

Ringworm of the Hands Though fungous infections of the hands are by no means rare this diagnosis is made with too great frequency The infection in this area has so much in common with infections of the feet that it need not be considered in any great detail There are two main types (1) the inflammatory vesicular and (2) the noninflammatory squamous The former is uncommon in temperate climates though dermatophytids associated with infections of the feet are common *Trichophyton mentagrophytes* is the organism usually recoverable from the acute vesicular type The course is one of spontaneous healing provided the hands are not subjected to constant chemical or traumatic irritation

Ringworm of the Scalp Tinea capitis is predominantly a disease of children and will not be considered in detail herein It is caused by a variety of fungi In cases which are transmitted from man to man and in which the most common causative organism is *Microsporum audouini* the course is one of great chronicity healing does not occur unless increased resistance of the host becomes evident in the form of inflammatory changes Such a local response may become quite severe and pro-

gest a fungating iododerma or bromoderma grossly or may even mimic the condylomas of secondary syphilis or the lesions of granuloma inguinale In this type as in exfoliative pemphigus the response to corticosteroid therapy may be poor and massive doses are often required

In another type of pemphigus not uncommon the distribution and morphology of the lesions is suggestive of a mixture of pemphigus seborrheic dermatitis and lupus erythematosus (Senear Usher syndrome) Erythematous scaling and crusted lesions develop on the nose and malar areas in a butterfly distribution and similar lesions with or without bullae may also appear on the anterior chest interscapular area and the scalp The mucous membranes show involvement only occasionally The general health of the patient is ordinarily good for some time after the onset of the disease The course of the eruption is insidious and slow but frank fatal pemphigus usually develops

Brazilian Pemphigus (Fogo Selvagem) This disease which is endemic in Brazil is clinically and *histologically identical with pemphigus foliaceus* The endemic nature of the disease makes it impossible to state with certainty that it is similar to pemphigus foliaceus since the latter has never been seen in endemic form in the United States or in Europe The best opinion would indicate that fogo selvagem is an infectious contagious disease About 3 000 cases are on record in Brazil and convincing evidence of transmission from person to person is available *The disease almost always begins before* the age of thirty is frequently associated with endocrine disturbances and does not involve the mucous membranes

Histologic Diagnosis The histologic features of common pemphigus are highly characteristic and the changes seen in smears or biopsies of early lesions are diagnostic There is a disturbance of the epidermal cells in which the fundamental change *is a disruption of the intercellular connections* of the epidermis (acantholysis) seen in either biopsies or material taken by a special scraping (see p 1743)

The course of pemphigus is variable The untreated patient may show occasional remissions but recurrences invariably develop each a little more severe than the previous one Death may occur from 2 to 3 months following the initial lesion or the disease may continue for years If corticosteroid therapy is not administered death within 2 years may be anticipated This occurs as a result of shock toxemia a cachectic state or some secondary complication such as septicemia or bronchopneumonia *It is important to keep in mind* that the skin and mucous membranes are the primary tissues involved and if these lesions can be controlled signs of systemic disease will remain absent or very moderate In uncontrolled pemphigus marked secondary anemia may develop Hypoalbuminemia may also be present because of the negative nitrogen balance resulting from loss of protein to denuded areas of skin and from *the inability of some patients to ingest* solid foods In widespread severe pemphigus the patients are extremely ill There may be a marked leukocytosis at times eosinophilia and the general picture is one of serious toxicity The temperature is ordinarily not markedly elevated unless extensive secondary bacterial infection has occurred Routine laboratory studies do not yield characteristic or constant findings However in advanced *cases the sedimentation rate is increased anemia is* constant the total serum proteins are almost invariably lowered and marked disturbance of serum electrolytes may be seen

Treatment Corticosteroid therapy is the only means by which true pemphigus may be controlled it is one of the few diseases in which such therapy is justified as soon as the diagnosis is established even though the presenting signs and symptoms are *mild Conditions which might ordinarily* be regarded as contraindications to corticosteroid therapy must often be waived if the diagnosis of pemphigus is established It is too early to suggest that actual cures of pemphigus have been achieved but considerable numbers of patients have been maintained in a state of remission for the several years since corticosteroid therapy became available As a rule such therapy must be continued indefinitely *very few patients have found it* possible to remain in remission in the absence of continued treatment

It is advisable to start treatment with rather large doses of corticosteroids the author prefers ACTH ordinarily in the gel form If the patient is critically ill ACTH in a dose of 25 to 40 units should be given daily by 8 hr intravenous drip In many patients subsidence of the eruption will be noted in a few days and reduction of the dose of corticotropin may then be possible ordinarily by lowering the daily dose to 15 to 20 units and then giving such a dose less frequently No set rules for this can be put down In some patients the dose may be reduced to a surprisingly low level as little as *10 or 15 units of ACTH every 2 weeks* If cortisone or its analogues are used the initial dose required may sometimes be so high as to be unfeasible economically However later in the course of treatment trial of such therapy may ordinarily be undertaken safely

The corollary medical and nursing care of extensive pemphigus is a formidable problem in some patients The supervision required is not dissimilar to that of an extensive burn and close check for evidence of local or systemic infection of protein and electrolyte balance and of the nutritional and hematologic status must be kept Blood transfusions



PLATE VI

(*Upper left*) Widespread mycosis fungoides This is the only lymphoma which produces characteristic skin lesions (*Upper right*) Leukemid eruption in a patient with rapidly fatal acute myelogenous leukemia This was the initial sign of illness The skin lesions showed no leukemic infiltrate (*Center left*) Severe seborrheic dermatitis with otiti e terna and secondary streptococcal infection (*Center right*) Longstanding blastomycosis The patient's general health was excellent (*Lower left*) Inflammatory tinea profunda (*Trichophyton mentagrophytes*) infection acquired from a co No systemic reaction The lesion involuted spontaneously (*Lower right*) Atopic dermatitis Involvement of the antecubital fossa and surrounding skin is characteristic The changes seen are almost entirely due to scratching and rubbing



PLATE V

(*Upper left*) Epidermoid carcinoma developing in scar of burn on lower leg. Any persistent ulcerative or proliferative process in a scar should be subjected to biopsy. (*Upper right*) Basal cell epithelioma. This is a relatively neglected lesion. Surgical excision was curative. (*Center left*) Chronic psoriasis and melanotic melanoma. In extensive chronic dermatoses the development of other significant unrelated skin lesions, particularly tumors, may easily go unnoted. (*Center right*) Severe bullous reaction to sulfathiazole. The lesions are very similar to those seen in pemphigus. This patient had been sensitized by previous prolonged topical sulfonamide therapy. (*Lower left*) Nodules of melanocarcinoma of scalp occurring around scar of previously excised nevus. Wide excision was not curative. (*Lower right*) Severe industrial contact dermatitis.

are sometimes of critical value If there is evidence of bacterial infection of the skin even in the absence of a systemic response it is rarely possible to control it by topical therapy *It is of the greatest importance* to conserve the accessible veins as much as possible because they may be few in number if the cutaneous lesions are extensive

Dermatitis and Eczema

Various types of acute and chronic dermatitis constitute over 50 per cent of all clinical dermatology While the changes in the skin follow a basic pattern which is reasonably constant the factors which may initiate or prolong a dermatitis are numerous

The morphologic changes of acute and chronic dermatitis are clear cut and not easy to confuse with other patterns of skin reactions The signs of dermatitis in the order of their evolution are as follows (1) erythema and swelling (2) oozing and/or vesiculation (3) crusting and scaling (4) thickening and evidence of repeated excoriation (5) hyperpigmentation scratch papule formation and lichenification The first three changes are those of an acute dermatitis the latter two are seen only if the process persists for several weeks or longer While there is no entirely satisfactory classification which will include all variants of a dermatitis eczema group of diseases some categorization is helpful Separate classification of a particular group is justified and helpful if one or more of the following criteria are satisfied (1) it is a type in which a definite cause can be determined (2) it occurs in a fairly regular pattern which (3) is helpful in determining the prognosis in the individual patient gives clear indication for certain types of treatments or indicates the need for further allergic and other medical studies The following main groups exist

Acute Contact Dermatitis In this type of dermatitis the change may be due either to primary irritation from toxic substances or to true allergic sensitization (see p 1162) Contact dermatitis is the prototype of all dermatitic reactions in the skin and by far the most satisfactory to manage therapeutically In a very high proportion of patients the responsible substance may be determined accurately and the cause removed It is essential that this be done as quickly as possible because persistence of the reaction will lead to trailing complications which may be self perpetuating

Atopic Dermatitis This exceedingly chronic dermatitis possesses distinctive features in respect to localization of lesions personal and familial evidence of allergy and a characteristic though often erratic course It produces more chronic disability than any other disease in which the chief manifestations are in the skin This plus the fact that the affected patient frequently has other evidences of atopy makes the disease of considerable medical importance In addition because corticosteroid therapy is often rapidly effective in relieving the inflammatory changes the problem of untoward physiologic effects arising from prolonged therapy of this type given for atopic dermatitis is assuming increasing importance Atopic dermatitis of and by itself is not a fatal disease but the suddenly developing complication of secondary infection by the virus of either herpes simplex or of vaccinia may sometimes lead to death

Seborrheic Dermatitis This form of dermatitis is also quite clear cut in respect to localization of lesions frequent association with evidence of sebaceous dysfunction increased vulnerability to secondary bacterial infection and a course which is often chronic In widespread forms it may be very disabling

Nummular Dermatitis This type of dermatitis has a distinctive morphologic pattern (nummular coinlike) The lesions are frankly dermatitic round and usually vary in size from 2 to 4 cm in diameter Low grade secondary infection is common The distribution is chiefly to the extensor surfaces of the extremities and the posterior shoulders and back though any site may be affected The dermatitis is most common in patients above middle age and may follow an acute contact dermatitis or occur as an id complication of chronic stasis dermatitis It is possibly seen more frequently in individuals with atopic backgrounds The causative factors are poorly understood but a psychosomatic component is often prominent The lesions commonly recur at the same site and the outlook for immediate cure of the disease is poor though permanent remission may ordinarily be anticipated eventually

Lichen Simplex Chronicus (Circumscribed Neurodermatitis) This is a clear cut and very common condition in which the changes are due almost *entirely to scratching and rubbing* The lesions are usually sharply circumscribed Any site may be affected but common ones are in the occipital region in women on the neck and on the lower legs Many cases of vulvar and anal pruritus fall into the group of circumscribed neurodermatitis The area involved becomes itchy either as a result of some preceding irritation or often without any previous lesion The scratch itch scratch cycle becomes firmly established Psychosomatic factors are often prominent and many patients frequently admit to indulging in scratching as a means of relieving nervous tension In such persons if the patch is not too troublesome such a lesion is probably to be preferred to some psychosomatic manifestation affecting another organ system

Stasis Dermatitis This is another clear cut type of dermatitis in which the basic etiologic factors are

scratching or from the application of skin irritants In atopic dermatitis a disease in which almost all of the changes in the skin are the result of excoriation and rubbing the antecubital area has a consistently increased sensitivity to itch stimuli while this is not the case in normal controls Continuation and elaboration of these studies gives promise of much better methods of evaluating the effectiveness of antipruritic agents and of understanding the variabilities of itching seen in the same disease occurring in different individuals

The remedies which are used for the relief of itching are legion In some of them a reasonable explanation of the mechanism of effectiveness is apparent while in others it is not The following statements may be made with some assurance

Topical agents whether local anesthetics or otherwise are least effective when the skin surface is relatively undamaged The absorption of local anesthetics from the skin is so minimal as to make it impossible to achieve adequate concentration in the underlying itch points If the integrity of the skin is disturbed there is some increase in effectiveness but it is still not as marked as might be desired Among the useful compounds are menthol and camphor Derivatives of Novocain are not advised because of their high sensitizing capacities most marked with Pontocaine Antihistaminics likewise have some local anesthetic properties but many of them are potent sensitizers and their clinical effectiveness on topical application is poor Topical agents for the relief of itching are much more effective on mucous membranes or at mucocutaneous junctions because of the significant absorption which will occur in these areas

In skin which is dry old or chapped very minor stimuli may induce paroxysms of itching Under such conditions a bland protective ointment or paste often has a good effect in preventing these stimuli from reaching the nerve endings Extremes of heat or cold likewise have some temporary good effect upon itching but should not be so drastically applied as to injure the skin

The antipruritic effects of topical steroid therapy e g hydrocortisone prednisone prednisolone are often marked particularly at mucocutaneous junctions so that such agents are very useful in vulvar and anal pruritus and in inflammatory conditions about the eyelids

The systemically administered compounds which will relieve itching are few The most striking of these are of course the steroids apparently acting through their antiinflammatory effects The physiologic risks of such therapy are such however as to make them justified only for very extensive and severe dermatologic processes They are probably most valuable and safe in short term conditions such as contact dermatitis or pruritic drug eruptions Antihistaminics are useful in frankly allergic conditions such as acute urticaria but have very limited effects in chronic dermatitis Tranquilizing agents such as *Rauwolfia* derivatives meprobamate and chlorpromazine may have moderate antipruritic effect in some patients but they are highly irregular in their effectiveness in this regard A phenothiazine compound trimeprazine has had wide investigational use in France and a limited application to date in the United States In the author s experience it has very marked antipruritic effects in some patients though its usefulness is somewhat limited by associated variable sedative effects In patients in whom topical therapy is ineffective and steroids are either unjustified or ineffective trimeprazine is well worthy of trial This is particularly true in infantile eczema atopic dermatitis and pruritus incident to diseases such as obstructive jaundice or Hodgkin s disease

Generalized Exfoliative Dermatitis

A chronic dermatosis which affects all or nearly all of the skin surface is a general medical problem of considerable importance and much difficulty Though examples of such conditions are seen in all age groups the incidence is highest in persons above middle age In some instances the early origins of the exfoliative dermatitis in terms of the type or etiology of the inflammatory changes are fairly clear Not infrequently however the generalized dermatitis arises for no apparent cause The changes may prove to be completely intractable especially in older patients

In the chronic phase of a generalized exfoliative process the skin is red thickened and scaling There may be oozing but vesicles are rarely seen A variety of disease conditions may give rise to this process It is fortunately very rare after acute contact dermatitis localized neurodermatitis nummular dermatitis and eruptions of the hands and feet Seborrheic dermatitis and atopic dermatitis may sometimes eventuate in a chronic exfoliative process Drugs may produce a chronic generalized reaction this was seen frequently when trivalent arsenical compounds were used in the treatment of syphilis Prolonged extensive contact with a sensitizing agent particularly an air borne one may occasionally induce an irreversible generalized dermatitis

Certain nevoid changes may produce chronic redness and exfoliation The most common of these are severe ichthyosis or congenital ichthyosiform erythroderma Psoriasis may at any age but most frequently in adults become completely generalized In this phase it is frequently accompanied by rheumatoid arthritic changes

In any patient with a generalized exfoliative process but particularly those above middle age

peripheral venous disease and tissue edema (see p 1339) It is important that prompt measures to control the dermatitis be undertaken before it has become severe and chronic Stasis dermatitis is characterized by greatly increased vulnerability to primary irritant or sensitization reactions to topical medication

These are the reasonably clear cut syndromes in the dermatitis eczema group There are three other well defined large groups as follows

Chronic Eczematous Dermatitis This is a group in which often the original cause and initial pattern of the disease have long been lost sight of and in which various secondary factors are playing a predominant role It is frequently the end point of a contact dermatitis in which the causative factor was not recognized promptly The extent and distribution of the dermatitis may vary greatly There are no constant associated systemic factors though sensitivity to particular foods or drugs must always be kept in mind In such patients there is temptation to use a wide variety of topical measures or to resort to systemic corticosteroid therapy without careful study of the patient as a whole and pains taking analysis of the various etiologic factors which might be playing a role including vasomotor disturbances sweating dysfunction low grade bacterial infection and psychosomatic factors

Infantile Eczema This is a classification based entirely on the age and the peculiarities of dermatitic reactions of the infantile skin These differ considerably from those of the adult

Chronic Dermatitis of Hands and/or Feet This is a classification based entirely upon the region involved but it is justified because it is such a common problem The etiologic factors are often complex Contact atopic and nummular dermatitis not infrequently are localized to the hands and feet Certain forms of psoriasis and of "id" reactions may appear in this fashion For all practical purposes superficial acute fungous infections may be included in this group This condition may be exceedingly chronic and at times highly disabling

Treatment of Pruritus

The means of relieving pruritus are on the whole much less satisfactory than those for the relief of pain In localized processes of acute nature the symptom is troublesome but relatively unimportant However in more extensive chronic inflammatory eruptions and in association with jaundice or with Hodgkin s disease the pruritus may be so severe and overpowering as to allow the patient to think of little else Though analgesics such as aspirin are of occasional small benefit potent analgesics such as morphine frequently increase itching apparently through the release of histamine from mast cells in the skin Sedatives and hypnotics may induce sleep in the patient but the itching continues unabated Much harm may result from poorly selected topical agents which produce irritation or sensitization e g phenol antihistaminics and compounds related to Novocain

Understanding of the phenomena of itching and the transmission of the itch stimulus has been greatly extended by the recent work of Shelley Arthur and others Until recently histamine was the standard material for inducing a measurable pruritus and this material was considered as the probable principal chemomediator of itching Shelley and Arthur postulated that an enzyme was concerned in the mediation of itching and have studied this intensively Severe itching may be induced by a wide variety of proteinases without the erythema and whealing seen following the injection of histamine Proteinases are available to the subepidermal cutaneous nerve endings from a wide variety of sources in cutaneous disease e g from infiltrates (leukopeptidases) from surface flora (fungous and bacterial proteinases) from the capillaries (plasmin) and from damaged epidermal cells (catheps ins) It has been shown that the antigen antibody reaction releases proteinases

The well established punctate nature of the cutaneous sensory system has been demonstrated to hold true for the itch receptors and itch points may be mapped on the skin either by chemical stimuli or by appropriate electrostimulation with microelectrodes The itch stimulus is transmitted at a conduction speed for the small unmyelinated slow (C) fibers Histologic examination of itch points shows them to consist of clumps of free unmyelinated nerve endings spread at a level just below the epidermis

On the basis of clinical observation it is well known that some diseases tend to produce pruritus while others do not some persons with itching diseases (i e lichen planus) itch while some do not itching tends to come and go often without any apparent relation to the morphologic changes in the skin while healing lesions frequently itch more than acute lesions

By the use of a standard itch stimulus Shelley and Arthur have shown that there is a marked variation in the itchiness of the skin of various parts of the body in the same patient and also considerable differences in the response of different subjects to the itch stimulus The hands are found to be a naturally itchy area though eczematous eruptions of the hands are characterized by remarkable variation in the amount of itching After acute exacerbations there is evidence that damage to the receptor nerve network has occurred On the basis of clinical observation it is apparent that the perianal and vulvar regions are also highly itchy and that this itching may be relieved temporarily by damage from

the possibility of a lymphoma must receive serious consideration Mycosis fungoides is frequently preceded prior to the development of frank skin tumors by a dry patchy dermatitis which with each recurrence becomes more severe and extensive Such lesions may recur for as long as a decade Repeated biopsies over a period of years may be required before the characteristic cellular infiltrate of mycosis fungoides is demonstrable

Senile involution of the skin may produce a severe and extensive erythroderma Such changes have been designated by a variety of terms based on morphologic variations but these are of little value to the general clinician The syndrome may be designated as *exfoliative erythroderma* and the patient then studied further for any dermatologic or general medical criteria which will provide a more useful and precise classification

Management Patients with generalized inflammatory exfoliative dermatoses deserve the most searching study They are often relatively or completely disabled and their appearance may bring about social ostracism

Biopsy of the skin often with repetition at intervals of weeks or months is an essential feature of the study of such patients The most careful hematologic studies are indicated In such patients varying degrees of generalized lymphadenopathy are almost always present either in response to the chronic inflammatory changes of the skin or as part of an underlying lymphoma Lymph node biopsy obviously will be required at times but should not be undertaken without due consideration because the healing after deep surgical biopsy is often very protracted especially in the inguinal or axillary regions Chemical studies of the blood with particular reference to serum protein levels and electrolytes may at times be revealing It is particularly important to keep in mind that the protein losses from exfoliation may be significant

The heat regulatory mechanisms of such patients are greatly disturbed A moderately cool environment may often induce a chill because of increased radiation from the vascular bed Because of the marked decrease in sweating which may be present sometimes amounting to complete anhidrosis increase in the environmental temperature is poorly tolerated and may induce febrile episodes

Skilled nursing care is of the utmost importance in such patients but may be a disagreeable and taxing task Topical therapy other than with very bland and inexpensive agents is not feasible As a rule petroleum or equal parts of water and Aquaphor or ordinary hydrogenated vegetable oils are best tolerated Care should be employed in the widespread use of compounds which may be toxic on absorption e g salicylic acid mercury phenol and strong concentrations of tar and resorcin

Systemic corticosteroid therapy is almost always indicated in patients with severe intractable exfoliative dermatitis but such therapy must sometimes be very prolonged In exfoliative psoriasis the author has found the steroid triamcinolone of considerable value in comparison with the steroids previously available Occasional transfusions of whole blood may be indicated Fever therapy by foreign protein injections is sometimes worthwhile The condition sometimes justifies a trial of x ray therapy preferably to a restricted portion of the skin initially This must be given with the greatest care and expertness however if extensive areas are to be exposed to ionizing radiation

Patients with generalized exfoliative dermatitis may be highly susceptible to infection of localized superficial type to cellulitis to deep cutaneous abscesses and to thrombophlebitis Intermittent or prolonged administration of appropriate antibiotics may be necessary

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Section 1 General Problems

267 GENERAL CARE OF THE PATIENT

One of the first decisions to be made with regard to medical management is whether the care of the patient is to be undertaken at home or in the hospital and whether the services of special nurses will be required The answer to these questions will depend on a number of factors the economic circumstances of the patient the character of his illness the facilities that will probably be necessary in the investigation and management of the illness the nursing problems likely to be encountered and the capacity of the attending personnel to handle them as well as the personalities of the patient and of those surrounding him

Regardless of the competence and experience of nurses or others who may be in attendance the management of the illness should be in the firm charge of the physician It is the obligation of the doctor to write orders with regard to all relevant details in so unambiguous a manner as to provide no foreseeable opportunity for confusion frequency with which vital signs are to be noted and recorded diet fluid intake rest and activity administration of drugs care of skin and mouth in certain cases and other matters essential to the welfare and comfort of the patient

The family and nurses should be instructed regarding possible untoward events that may occur in the course of the illness or as the result of the administration of drugs or other forms of therapy This is important not only because prompt measures may be taken to counteract the harmful or disagreeable consequences but also because the patient and his family are less likely to be alarmed or resentful if forewarnings have prepared them for unpleasant episodes that might otherwise have been considered the result of negligence or thoughtlessness

Control of Body Temperature Since fever ordinarily does little harm and imposes no great discomfort antipyretic drugs are rarely necessary and may obscure the effect of a specific therapeutic agent and of the natural course of the disease There are situations however in which lowering of the body temperature is of vital importance heat stroke postoperative hyperthermia delirium due to high pyrexia shock associated with fever Under these circumstances sponging the body surface with alcohol or the application of cool compresses to the skin and forehead may be employed When high internal temperature is combined with cutaneous vasoconstriction as in heat stroke or postoperative hyperthermia the cooling measures should be combined with massage of the skin in order to bring blood to the surface where it may be cooled Immediate immersion in a tub of ice water should be considered a lifesaving emergency procedure in patients with heat stroke if the internal body temperature is in excess of 108 F

If antipyretic drugs such as aspirin (0 3 to 0 6 Gm) are employed to bring about a fall in temperature the ill effects of the unpleasant diaphoresis sometimes associated with an alarming fall in blood pressure and the subsequent return of fever occasionally accompanied by a chill can be mitigated by enforcing a liberal fluid intake and by administering the drug regularly at 3 or 4-hr intervals

Rest and Activity In general the position that the patient takes in bed and the strictness with which bed rest is enforced will depend on what is most comfortable for the patient Barring those disorders such as acute febrile illnesses shock and other conditions discussed in context where recumbent bed rest is obligatory it is advisable to permit activity outside the bed as soon as the patient s strength permits Permitting the patient to use a bedside commode or to walk to a nearby toilet will usually involve less expenditure of energy than will the often futile struggle on a bedpan Unnecessary insistence on prolonged bed rest favors the development of venous thromboses in the lower extremities with the risk of pulmonary embolism decalcification of bone with the hazard of nephrolithiasis development of decubitus ulcers loss of strength and the greater likelihood of postural hypotension hypostatic pneumonia to say nothing of the corrosive effect on the patient s morale These risks are greater in the elderly patient As his weakness increases as the result of inactivity and his desire to bestir himself consequently diminishes it may require firm persuasion to convince him that increasing physical activity is essential

Bladder Function Patients confined to bed often have difficulty of urination and may even develop retention because of a variety of factors inability to void in the horizontal position excessive use of sedatives and narcotics adrenergic drugs such as ephedrine and antihistamines overdistention and

of abdominal distention due to aerophagia have been described in Chap 5 When this condition is present the most urgent decision is whether it requires surgical intervention If it is decided that the cause does not require immediate surgical correction measures should be instituted at once to correct contributing factors such as the hypoxia of pneumonia or fluid and electrolyte imbalances from a variety of causes especially potassium and sodium deficits or intracellular fluid excess Nasogastric intubation with a No 18F Levin tube and decompressive suction should be started at once Machine suction of the Gomco type is now generally preferred Regular irrigation of the tube preferably with bicarbonate solution is necessary to dissolve mucous plugs Plastic tubes are better tolerated than rubber tubes if prolonged intubation is required the tube should be changed about once a week Patients undergoing gastric suction may lose enormous quantities of gastric juice containing chloride potassium sodium and water requiring parenteral replacement Thirst is frequently present and there is a great temptation to permit the ingestion of fluids by mouth but this is a grievous mistake for ingested water leads to further loss of electrolytes as it is returned by suction Once fluid and electrolyte balance has been achieved thirst is rarely a problem

The greatest usefulness of the long double lumen tube or Miller Abbott tube is for preoperative decompression of the gastrointestinal tract of the patient with mechanical ileus a problem of surgery rather than of internal medicine In the event a Miller Abbott tube is selected and passed into a patient with paralytic ileus it is frequently necessary to pass a short Levin tube through the opposite nostril to maintain gastric decompression as the long tube descends into the small bowel However the long tube is not usually applicable for the patient with paralytic ileus because it does not pass when peristalsis is absent and is not needed if peristalsis has returned

It is rarely necessary for nasogastric decompression to be continued for more than 3 to 5 days Indeed *failure to relieve distention within 12 to 18 hr should call for a complete review of the problem and consideration of a surgical approach to it*

There are numerous tube designs to meet special purposes Alimentation by tubes is often necessary the route may be gastric or jejunal Jejunal alimentation is possible through extremely small plastic tubes No 6 to No 10F with the advantage of lessened nasal discomfort and irritation Small tubes of this sort may often be passed through esophageal or pyloric strictures and remain patent and well tolerated for weeks or months

A supplementary procedure of some usefulness in the treatment of established and severe distention is the administration of oxygen by the BLB mask The principle underlying this procedure is the removal of the predominantly nitrogen fraction of intestinal air Nitrogen transport in the blood is limited by solubility Hence elimination of nitrogen during inhalation increases the opportunity for nitrogen absorption from the bowel

Smooth muscle stimulants such as Pituitrin and Prostigmine are not recommended The former is potentially dangerous and the latter unnecessary when intubation and fluid management have been carried out intelligently Enemas serve no useful purpose

268 NUTRITION
Harold Brown

In the well nourished individual with an illness of short duration the problem of nutrition during illness is of minor importance one can usually follow the vagaries of the patient s appetite On the other hand in the patient debilitated by a long or severe bout of illness the physician is faced with the problem not only of maintaining his patient s state of nutrition but also of bringing about a return to the normal nutritional state The problem may be complicated by the patient s inability to take food by mouth because of anorexia weakness mechanical disturbances in the gastrointestinal tract or the state of consciousness

On occasion the depletion has been caused by the socioeconomic state of the individual food fads addiction to drugs or alcohol or psychiatric disturbances

Nutritional Requirements The nutritional requirements must be thought of in terms of calories proteins minerals and vitamins Fluids and Electrolytes are discussed in Chaps 48 and 49 and Gain and Loss of Weight Chap 21

The caloric requirements of the patient are derived from the basal metabolic requirement plus 30 per cent for bed activity and 8 per cent for each degree Fahrenheit of fever The basal caloric requirement is proportional to the individual s surface area which can be estimated from the height weight nomogram of DuBois (see Fig 206) For this calculation the "ideal weight or what the patient should weigh should be used The average surface area for adults is 1 6 sq m for women and 1 8 sq m for men The heat production per square meter of body surface diminishes progressively with age being 50 cal per hr at the age of ten to twelve years and about 32 cal per hr at the age of ninety years For the great majority of normal adults however the total basal heat production is

decompensation of the bladder due to the administration of large quantities of fluid The brisk diuresis following a mercurial injection may cause acute urinary retention in a person with mild subclinical prostatic obstruction

If the patient is not too ill permitting him to stand in the upright position may be all that is necessary to start the flow of urine or an enema of hot soapsuds or glycerin and water or the administration of neostigmine (Prostigmine) 0 5 to 1 0 mg hypodermically may be effective Because of the risk of infection especially in diabetic patients catheterization should be employed only when unavoidable Often but one catheterization is required in which case sulfisoxazole (Gantrisin) 0 5 Gm four times daily should be given as a prophylactic therapy for 2 or 3 days When urinary retention persists one may be compelled to resort to an indwelling catheter though infection is certain to occur if it remains in the urethra 72 hr or more In this case the bladder should be irrigated several times a day with an aqueous solution of benzalkonium chloride (Zephiran) in a dilution of 1 20 000 Since it is impossible to clear the bladder of infection in the presence of an indwelling catheter antimicrobial therapy should be deferred until the catheter has been removed in order to minimize the risk of establishing a proteus or resistant staphylococcus as the predominant organism After a few days when bladder compensation has been restored and the catheter removed antimicrobial therapy should be instituted and continued until urinary examination indicates that all traces of infection have disappeared

When the bladder is paralyzed because of neurologic disease a system of tidal drainage or drainage through a suprapubic cystotomy may be preferable to a constant or intermittent drainage through an indwelling catheter Zephiran 1 20 000 is used as the irrigating fluid

Constipation This is a common problem in individuals who are forced to limit their diet and activities Inadequate fluid intake especially in hot weather is a frequent important contributing factor A helpful and harmless method of overcoming constipation is the administration of a wetting agent dioctyl sodium sulfosuccinate (Velmol Colace or Doxinate) 150 to 200 mg each day alone or in conjunction with a vegetable mucin (Metamucil) 1 tsp daily Occasionally supplementary doses of a mild laxative such as milk of magnesia cascara or phenolphthalein may be required Because of the risk of lipoid pneumonia mineral oil preparations are best avoided especially in elderly patients or those suffering from neurologic disorders that interfere with the swallowing mechanism Fecal impaction is likely to occur in older or paralyzed patients and in those to whom sedatives narcotics barium or aluminum gels are being given A rectal examination should be made if the patient complains of rectal pain and inability to expel a stool or even if he states that small amounts of stool are being passed Should an impaction be found manual removal preceded by repeated small oil instillations may be necessary

Diarrhea Diarrhea that occurs in the course of a transitory illness will usually respond to a low residue diet aluminum hydroxide gels and when needed 1 or 2 tsp paregoric after each bowel movement When the diarrhea is more severe powdered opium 0 06 Gm or morphine sulfate 0 015 Gm every 4 to 6 hr and replacement of fluid and electrolytes will be required

Nausea and Vomiting Any obviously remediable cause should be corrected at once Frequently however the cause is obscure or cannot be controlled immediately and palliative measures may be required When the symptoms are severe chlorpromazine (Thorazine) should be administered 25 to 50 mg intramuscularly with an equal quantity of 2 per cent procaine to reduce the pain caused by the drug Thereafter 25 to 50 mg chlorpromazine may be given orally or by rectal suppository about four times daily Since the use of chlorpromazine may be attended by a significant fall in blood pressure the patient should be instructed to remain in the recumbent posture for about an hour after it has been given parenterally Other side effects especially sedation may occur and appropriate warnings should be given Because of the risk of jaundice and agranulocytosis the drug should not be given indiscriminately and when the symptoms are not urgent other drugs may be tried even if they are somewhat less effective The best of these are prochloperazine (Compazine) 5 to 10 mg four times daily meclizine (Bonamine) 25 to 50 mg twice daily or promethazine (Phenergan) 12 5 to 25 mg two or three times a day Meclizine is particularly efficacious when the nausea is caused in part by increased vestibular sensitivity as when it follows the administration of opiates or is brought on by motion sickness

Gastric irritation which may have been an initiating factor or may have developed subsequent to the vomiting may be decreased or controlled by swallowing sips of warm water tea bouillon or bland antacid preparations (Gelusil Basaljel) Food other than the liquids mentioned above should be withheld for 24 to 48 hr in the more severe cases later small servings of a bland diet may be permitted In a small percentage of cases the prompt correction of fluid and electrolyte deficits may be essential

Abdominal Distention Air swallowing or aerophagia is responsible for practically all the gas in the gastrointestinal tract The harmful consequences

ing the day and continuous drip feedings during the sleeping hours

Gavage should be used only with extreme caution in patients with esophageal varices and in patients who have lost their gag reflexes The tube should be irrigated daily and may remain for as long as a week

Sometimes diarrhea is occasioned by the high caloric formula This may be controlled by cutting down the amount of fat or adding applesauce or commercial pectin

For gavage or oral feeding mixtures extremely high in protein and calories can be devised by using casein or one of the many dried milk powders along with the usual cream and egg milkshakes Some of the dried milk powders (Lonalac Lesofac) have been made extremely low in fat and/or sodium chloride without too much loss of their palatability A wide variety of formulas is available depending upon the particular purpose of the supplement Commercially prepared mixtures (Calorigen Sustagen) for oral supplements or gavage feeding are now available These mixtures are sterile and will not clog the small nasogastric tube They contain adequate concentrations of protein calories and electrolytes to meet the patient s nutritional needs For short periods of feeding simpler liquids such as plain milk or eggnogs may be administered In the home it is possible to homogenize a complete meal with a Waring Blendor and to feed this material through a tube This will ensure a well balanced diet and avoid the necessity of making up separate formulas

It is well to add vitamin supplements for the malnourished patient The usual practice is to give five to ten times the recommended daily allowance of the factors which seem grossly deficient and one to five times the required amount of the other factors since in most cases there are multiple deficiencies even though there may seem to be a lack of only one specific factor A more detailed discussion of the symptomatology and treatment of deficiency disease is found in Chaps 55 to 59

Parenteral Feeding The oral route for alimentation has the obvious advantage of allowing the patient to take in a well rounded diet in much larger quantities than the parenteral route The latter however is often needed to supplement the patient s nutrition As the sole means for administration of food the parenteral route is imperfect It is extremely difficult to supply an individual s complete protein and caloric needs in this way Parenteral nutrition should be thought of in several categories In the first category there is the patient whose oral intake will be interrupted for periods up to one week and who can withstand some tissue loss In this patient the failure to supply adequate calories will mean varying degrees of adipose tissue loss Studies of rations for life raft survivors have indicated that about 100 Gm of glucose per day will afford almost a maximum nitrogen sparing action In this type of patient not much is gained by giving more than 100 Gm of glucose per day plus the needed fluids and electrolytes Additional glucose or other sources of calories will only conserve the body s fat stores In this situation there is probably little need for supplying protein or amino acids in an attempt to maintain the nitrogen balance

In the patient who is more debilitated or who must be maintained with parenteral feedings for longer periods one should attempt to establish caloric and nitrogen balance For this purpose there are available solutions of glucose fructose invert sugar (glucose and fructose) ethyl alcohol and amino acids The sugars and amino acids supply approximately 4 calories per Gm while alcohol supplies 6 calories per Gm

Glucose cannot be used in much higher concentrations than 10 per cent solutions without incurring a high incidence of phlebitis after a few days of administration In situations where the fluid intake must be rigidly restricted as in acute renal failure 30 to 50 per cent glucose solutions can be administered through a small plastic catheter which has been passed into a larger vein It is doubtful whether fructose solutions are more readily assimilated than glucose solutions by patients whose glucose tolerance is decreased by severe illness or diabetes as has been claimed

Ethyl alcohol can be used in 5 or 6 per cent solutions In addition to the sizable caloric supplement the alcohol will provide the usual psychic effects which may be beneficial to the patient with pain The alcohol solutions are given with glucose and/or amino acids It is probably safe to give up to 200 ml of 95 per cent alcohol by slow intravenous infusion over a 24 hr period without producing intoxication Alcohol should not be administered to the unconscious patient

Amino acid solutions (5 per cent) are readily assimilated sources of tissue nitrogen Numerous excellent preparations are now available and are free of side reactions if given more slowly than 300 to 400 ml per hr

Satisfactory emulsions of fat for parenteral administration have not been prepared

The uses of plasma whole blood and serum albumin are discussed elsewhere (p 1760)

The patient who is being fed via the parenteral route should receive therapeutic doses of vitamins

The problem of parenteral feeding is considerably simplified by proper attention to details such as the use of sharp needles avoiding the use of markedly hypertonic solutions and using veins distant from the elbow so that the patient may move

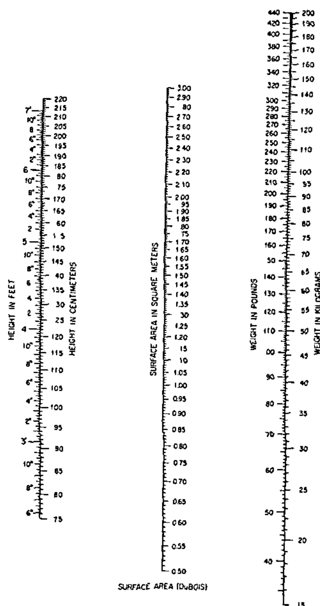


Fig 206 Nomogram for calculating surface area (*Du Bois Basal Metabolism in Health and Disease" Phila delphia Lea & Febiger*)

reasonably constant and ranges from 1400 to 1800 calories per day The average hospital diet will contain about 2000 calories

The recommended daily allowance for protein is set at 1 Gm/kg/day This is a generous allowance but in depleted states it may take three to five times as much to satisfy the protein needs Protein feeding in special situations such as acute renal failure nephrosis liver disease and other conditions is discussed in the appropriate chapters

The recommended daily allowances for vitamins in adult nutrition are tabulated in Chap 21 (p 184)

Vitamin K may be necessary in patients with impaired fat absorption Two to five mg per day of a water soluble preparation subcutaneously will make up the deficit Vitamin B_1 and folic acid should not be used without specific indications lest an underlying megaloblastic anemia be masked

Oral Feeding The sick patient all too frequently cannot take the full diet by mouth and one is faced with the problem of devising a diet which will suit the needs of the patient and yet be palatable to him

The dietitian can be of invaluable assistance in this situation Sometimes by more frequent smaller feedings plus supplements after the regular meal hours the patient s intake can be increased considerably The supplementary feedings can add many calories by utilizing nonsweetening carbohydrate such as lactose and by using additional fat in the form of cream and eggs or an oral fat emulsion (Lipomul Oral Ediol) Such a special diet should provide soft or liquid low residue meals which will reduce the need for mastication and limit the total bulk At times the caloric intake may be considerably increased by substituting high caloric vegetables such as peas and rice for those of negligible caloric content such as lettuce and cucumbers Eggnogs frappes and custards are frequently appealing and valuable supplements for a patient with a marginal oral intake

Both the physician and the dietitian must exercise considerable ingenuity in getting the patient to eat the prescribed foods An effort should be made to give the patient foods he will like and to serve them in an appealing fashion Unpleasant procedures or visits should not be scheduled at such a time that the patient will be emotionally upset during the meal period The size of the portions should be in accord with what the patient can consume so that he will not become discouraged at his inability to finish his meals For some individuals the use of wines or other alcoholic beverages for their stomachic qualities is beneficial

Gavage For the extremely weak anorectic or uncooperative patient tube feeding may be used with a small (2 to 3 mm) soft rubber or better still polyethylene or polyvinyl catheter There is little irritation from the nasogastric tube The liquid formula can be injected at intervals or as a continuous drip The former method is to be preferred for the attendant or nurse can aspirate any gastric residue before injecting 100 to 200 ml every 1 to 2 hr thus preventing gastric dilatation This technique also allows the diet to be kept in the refrigerator and avoids the possibility of bacterial contamination which is a distinct hazard with protein rich solutions On the other hand the constant drip procedure requires minimal nursing care and allows for alimentation over the entire 24 hr Simple devices can be arranged to keep the formula reservoir chilled Intermittent gavage can be used dur

should be crushed to ensure proper absorption or sodium barbital should be substituted Chloral hydrate (1 0 Gm) given with fruit juice at bedtime is also effective and may be substituted for the barbital if desired

Patients with serious mental agitation delirium or excitement who require prompt easily controlled relatively safe sedation should receive paraldehyde 15 to 30 ml by mouth in iced fruit juice or the same dose by rectum but diluted with 200 ml physiologic saline solution or 120 ml olive oil Generally it is wise to avoid the use of the barbiturates in highly agitated patients since occasionally they may precipitate serious mental confusion excitement or even manic tendencies Chloral hydrate 1 0 to 2 0 Gm by mouth or rectum is useful in the management of these individuals and frequently proves more satisfactory than the barbiturates

A word of caution about oversedation is wise in any discussion of sedative drugs All too frequently they are abused in that they are given when not needed the dose is too great or the wrong preparation is used They are a common source of constipation lead to fatigue and lack of energy and strength and interfere with the patient s recovery from his illness

When large doses of the quicker acting barbiturates 0 4 to 0 6 Gm daily are given for more than a week or two there is real danger of habituation which once it has developed is pernicious in character Withdrawal unless done skillfully and in graded steps may cause serious mental disturbance or precipitate convulsions The patient should not be encouraged to use sedative drugs as a crutch on which to limp through life One should search out and correct the underlying difficulty using sedation when necessary as a temporary helpful tool

PAIN

This sensory experience is unquestionably the most important signal of disease and serves a basic biologic principle that of preserving the life of the organism There are times however when it outlasts the disease to which it calls attention and giving rise to fear anxiety depression irritability and nervous exhaustion becomes detrimental unless relieved

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Occasionally integumental and deep pains of skeletal structures are of such severity as to require more powerful narcotic analgesics such as meperidine hydrochloride (Demerol) in doses of 50 to 100 mg orally or intramuscularly methadone hydrochloride 5 to 10 mg orally or subcutaneously or dihydromorphine hydrochloride (Dilaudid) 1 0 to 2 0 mg orally or subcutaneously These drugs are most useful in conditions when sedation is not required When pain is unusually severe and some degree of euphoria is desired morphine is the ideal drug It should be given in doses of 8 0 to 15 0 mg orally or subcutaneously Frequently a dose as small as 4 0 to 6 0 mg will relieve pain without causing undesirable nausea and vomiting If the original dose is too small a second dose of the same or slightly larger size can be given in 2 hr This divided dose is less likely to induce nausea and vomiting than the larger single dose because the stimulating effect of the first dose is insufficient to produce these symptoms and the depressant effect which follows reduces the sensitivity of the vomiting mechanism or renders it refractory to the second dose Since all these narcotic analgesics are for the most part detoxified by the liver they either should not be used or should be given in only half the usual dose in cases of liver disease myxedema adrenal insufficiency and other states in which the metabolic rate is reduced Morphine and related narcotic analgesics tend to cause pruritus and therefore should be used with care in patients with skin irritability The possibility of initiating addiction in susceptible individuals must be carefully evaluated in every instance

If the patient exhibits mental tension insomnia and restlessness a sedative drug such as pheno-

his arm about Ordinarily an infusion of 1 to 2 liters is given over a period of 3 to 6 hr and when additional infusions are needed the needle is inserted in another vein Flexible polyethylene tubing which may be inserted through special thin walled needles seems to lessen the tendency to thrombophlebitis when solutions are administered over prolonged periods The tubing may be kept in the vein for several days On the rare occasions when it is necessary to give markedly hypertonic solutions the polyethylene tubing may be threaded into a larger vein such as the vena cava In this location the hypertonic solutions are rapidly diluted by the large volume of blood flowing by so that phlebitis is avoided

Hypodermoclyses are little used in adult practice because hypertonic solutions are not readily absorbed Furthermore since the solutions must first equilibrate with the extracellular fluid this type of administration is not so pleasant for the patient as intravenous therapy

Parenteral feeding should be maintained only as long as is absolutely necessary Usually the patient s own appetite is an excellent guide but one should avoid the possibility of producing nausea and vomiting by too enthusiastic resumption of oral intake after a long abstinence It is well to begin with easily digested liquids and soft solids in small feedings which can be taken as tolerated before going on to the regular diet As the oral intake increases the parenteral feeding can be cut down

Adjuvants Testosterone propionate 25 mg every other day and related androgens are sometimes useful for increasing the positive nitrogen balance in the sick Corticotropin and adrenocorticosteroids have a nonspecific appetite stimulating effect which has been of value in some situations where impaired appetite is a major problem as in hepatitis Regular insulin in 5 to 10 unit doses 20 min before meals has also been used to stimulate the appetite

269 SEDATION AND RELIEF OF PAIN

SEDATION

As a consequence of many disease states patients frequently develop nervous tension anxiety irritability restlessness or insomnia In the young nervous tense restless individual the mildly sedative action of 15 to 30 mg phenobarbital given after meals and at bedtime for 3 to at most 14 days will do much to bring about relaxation while more definitive measures are being initiated If apathy or weakness occurs the drug should be stopped or the dose reduced one half Bromisovalum (Bromural) 0 3 Gm after meals may be tried if phenobarbital is unsatisfactory Older patients in this category requiring mild sedation seem to do better on small doses of chloral hydrate 0 25 Gm after meals and at bedtime Chloral hydrate should not be given to patients with any degree of gastric distress because of its irritant properties but with this exception it may be used with good results in almost any situation

In general there are three varieties of wakefulness For best management treatment should be based on the type exhibited by the patient In younger patients the most frequently observed type of insomnia is the inability to fall asleep These individuals have developed more and more tenseness during the day and are unable to relax This type of insomnia usually lasts from 1 to 3 hr and then the individual sinks into an exhausted deep sleep which continues through the night For these patients a quickly acting fairly rapidly destroyed hypnotic such as secobarbital (Seconal)—0 1 Gm given 15 to 20 min before going to bed—is desirable

The second group consists of patients who are able to go to sleep but who awaken in 1 or 2 hr and lose sleep in the middle of the night Some are alternately awake and asleep all night Often these are sick individuals with a debilitating or painful illness who develop more pain and restlessness as muscles relax leaving painful areas unsplinted In others fever sweats dyspnea or other distressful symptoms develop and demand attention Frequently these patients secure good relief from 0 1 Gm pentobarbital (Nembutal) given at bedtime In cardiac patients who have Cheyne Stokes respiration or moderate orthopnea a rectal suppository of aminophylline 0 5 Gm given at bedtime will frequently relieve the respiratory distress and promote sleep When pain is a factor in insomnia acetylsalicylic acid (0 3 to 0 6 Gm) should be given with the sedative Occasionally codeine phosphate (30 mg) may be required when pain is severe

The third group of insomnia patients consists of those who go to sleep promptly and sleep well most of the night only to awaken too early in the morning Most of these individuals are older people who turn night into day They go to bed and get up earlier and earlier so that soon they are sleeping during the day and are alert during the night Into this category also fall those individuals who are under great tension worry or anxiety or are overworked and exhausted These people sink into bed and sleep through sheer exhaustion but around 4 or 5 A M awake with their worries and are unable to get back to sleep Most of these patients are benefited by barbital (0 3 Gm) given with fruit juice or milk at bedtime For debilitated patients the compressed tablet of insoluble material

should be crushed to ensure proper absorption or sodium barbital should be substituted Chloral hydrate (*1 0 Gm*) given *with fruit juice at bedtime* is also effective and may be substituted for the barbital if desired

Patients with serious mental agitation delirium or excitement who *require prompt easily* controlled relatively safe sedation should receive paraldehyde 15 to 30 ml by *mouth in iced fruit* juice or the same dose by rectum but diluted with 200 ml physiologic saline solution or 120 ml olive oil Generally it is wise to avoid the use of the barbiturates in highly agitated patients since occasionally they may precipitate serious mental confusion excitement or even manic tendencies Chloral hydrate 1 0 to 2 0 Gm by mouth or rectum is useful in the management of these individuals and frequently proves more satisfactory than the barbiturates

A word of caution about oversedation is wise in any discussion of sedative drugs All too frequently they are abused in that they are given when not needed the dose is too great or the wrong preparation is used They are a common source of constipation lead to fatigue and lack of energy and strength and interfere with the patient s recovery from his illness

When large doses of the quicker acting barbiturates 0 4 to 0 6 Gm daily are given for more than a week or two there is real danger of habituation which once it has developed is pernicious in character Withdrawal unless done skillfully and in graded steps may cause serious mental disturbance or precipitate convulsions The patient should not be encouraged to use sedative drugs as a crutch on which to limp through life One should search out and correct the underlying difficulty using sedation when necessary as a temporary helpful tool

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barbital or sodium barbital may be given with the analgesic agents Sedative medication especially the quick acting barbiturates should not be used alone for the control of pain because they sometimes cause excitement and confusion under these circumstances

Visceral pain originating in the stomach gall bladder intestines or heart is usually very poorly controlled by the nonnarcotic analgesics Various combinations of acetylsalicylic acid and acetophenetidin usually prove to be ineffective unless given with sedatives The narcotic analgesics are the agents of choice but of course should never be given until the physician is certain that the relief of the pain will not mask the state of his patient If sedation is not desirable and if constipation is a troublesome problem the newer synthetic analgesics meperidine (Demerol) in doses of 50 to 100 mg orally or intramuscularly or methadone 5 to 10 mg by mouth or subcutaneously every 4 to 6 hr are recommended Like morphine these drugs are habit forming but they do not share with morphine the properties of strong analgesia sedation and euphoria Patients with severe visceral pain who are also *anxious or fearful and unable to* relax or sleep should be given morphine sulfate in doses of 8 to 15 mg subcutaneously The well known spasmogenic effects of morphine are partially counteracted by atropine sulfate 0 3 to 0 4 mg Aminophylline 0 5 Gm intravenously overcomes much of this undesirable spastic action a rectal suppository of 0 5 Gm although less effective may be substituted

Intractable pain due to incurable diseases such as metastatic carcinoma is one of the most difficult of therapeutic problems As a rule one resorts to narcotic drugs because of their strong analgesic action and habituation is accepted as the lesser of two evils An alternative is pain relieving surgery Section of peripheral nerves the lateral spinothalamic tracts in the spinal cord (cordotomy) or the lateral part of the medulla and lobotomy are relatively safe procedures which have advantages in certain cases over the continuous use of opiates

Section 2 Some Special Problems

270 BLOOD TRANSFUSIONS

Uses of Blood Transfusion By far the most important and most frequent uses of *whole blood transfusion* are to restore blood volume after hemorrhage trauma or burns and to maintain the concentration of circulating hemoglobin at an adequate level *in those types of anemia which cannot be re*lieved by specific measures such as liver or iron therapy

The extent to which blood may be lost when hemorrhage occurs within a viscus or a muscle mass *is frequently underestimated* Likewise it is not easy to judge the degree to which plasma has been depleted by leakage or how many red cells have been lost by hemolysis after a severe burn Severe arterial hypotension following a traumatic injury or an event suggesting the possibility of a concealed hemorrhage in the absence of evidence of other causes is indicative of a blood volume deficit exceeding 30 per cent i e 1 500 ml or more When the blood volume deficit is 20 per cent or less *patients are* unlikely to exhibit marked hypotension as long as they remain in the horizontal position In general it may be said that it is more common to underestimate than to overestimate the amount of blood needed in the management of shock and to restore blood which has been lost

Blood Substitutes It should be emphasized that no substitute for whole blood has been found which is in any way comparable to the value of the red corpuscles and plasma However if whole blood is not available to restore blood volume substitutes must be employed in emergencies Of these blood plasma is the best and in the dry form can be *transported easily and kept ready at hand* but the danger of transmitting the virus of homologous serum hepatitis is so great that the use of pooled plasma cannot be recommended Next in order of effectiveness is serum albumin which has a physio*logic effect* closely approaching that of plasma However it is very expensive For this and other reasons much attention has been given to the development of plasma expanders substances of such physicochemical properties that they will overcome the disparity between the capacity of the circulatory system and the circulating blood volume that exists in shock Of these the gelatins possess the fewest disadvantages but dextran a biosynthetic polysaccharide has been found to be very effective and is being used more and more Polyvinylpyrrolidone (PVP) is a colloid produced by the chemical combination of formaldehyde and acetylene which has some merit It should be borne

in mind that the plasma expanders should be employed only for the immediate emergency rather than repeatedly

When shock is clearly not due to blood loss transfusions are often withheld on the ground that such treatment is futile and may be dangerous Nevertheless where doubt exists concerning the nature of the shock whether oligemic or nonoligemic the administration of whole blood plasma or packed cells is justified and is not likely to be harmful In nonoligemic shock pressor amines such as norepinephrine have been found useful but such agents have been effective as interim therapy even in oligemic shock until whole blood could be obtained The uses of these agents are discussed in Chap 271

In the management of anemia other than that due to the acute loss of blood blood transfusions are commonly used more generously than is necessary or desirable The discovery of such anemia calls for careful study to determine its cause as discussed fully elsewhere (Chap 212) rather than the blind administration of blood Thus there is no justification for blood transfusion in iron deficiency anemias or in the macrocytic anemias with megaloblastic bone marrow unless the anemia is extremely severe or unless surgical measures must be carried out at once The patient who has such anemia has become adjusted to it and the sudden change produced by transfusion is unnecessary A physiologic response can be achieved by oral iron therapy or vitamin B_{12} or folic acid administration according to the nature of the deficiency Again in anemia associated with infection or in the management of the anemia of leukemia Hodgkin s disease or other disorders the treatment of the underlying condition whenever possible is preferable to blood transfusion Even in the management of aplastic anemia or other forms of anemia for which no specific therapy is available it is better to give only enough transfusions to maintain the hemoglobin at a level consistent with reasonable activity rather than to attempt to maintain a normal level Thereby the risk which each transfusion presents is reduced and the accumulation of iron in the tissues is less Such patients are often maintained quite satisfactorily at hematocrit levels between 35 and 40 ml per 100 ml blood

Whole blood plasma or albumin can be used to restore the colloid osmotic pressure of plasma to physiologic levels in cases of hypoproteinemia Intravenous injections of salt poor human serum albumin are particularly valuable in certain patients with hepatic cirrhosis and ascites the nephrotic syndrome idiopathic hypoproteinemia and the edema of malnutrition

As a means for providing protein nutrients in patients restricted to parenteral feeding other than as a temporary measure intravenous injections of whole plasma or of serum albumin are impractical This is because of their colloid osmotic activity and the consequent expansion of the recipient s plasma volume Whole blood is even less valuable as a protein nutrient in spite of its high protein content This is not only because of the expansion of the patient s plasma volume thereby but also because the contribution of the protein in the red corpuscles to the protein metabolic pool must await the natural destruction of the red corpuscles

There is no sound basis for the use of transfusions in the management of the great majority of infections It is true that blood transfusions have been employed effectively for the transfer of specific immune antibodies from convalescent donors to susceptible contacts where measles mumps and yellow fever have been present in epidemic form and immune transfusions have been considered to be of value in treating certain infections notably herpes ophthalmia and scarlet fever However other methods are now available for the management of most of these conditions Of the blood derivatives it should be mentioned here that gamma globulin is an important agent in measles prophylaxis and in the prevention of infectious hepatitis

Whole blood transfusions plasma or plasma fractions also can provide specific clotting factors which may be lacking in certain patients such as antihemophilic globulin (fraction I) prothrombin factors V (Ac globulin) and VII (spca) and fibrinogen Fresh normal plasma is capable of restoring all clotting factors and is particularly necessary for supplying factor V and the antihemophilic factor Stored plasma can be depended on only for prothrombin factor VII the plasma thromboplastin component (PTC) and fibrinogen When equipment constructed entirely of plastic or coated material is used fresh blood transfusions may also serve temporarily for the successful transference of blood platelets from one person to another As a method of treating conditions where leukocytes are needed this procedure is as yet neither practical nor very successful

Finally the removal of blood possessing pathogenic properties and its replacement with normal blood (exchange transfusion) is a valuable procedure in special circumstances as for example in certain cases of hemolytic disease of the newborn (erythroblastosis fetalis)

Although additional therapeutic benefits have been ascribed to blood transfusions their value and therapeutic rationale remain unproved Their use to pep up a patient who is not anemic and whose blood volume is normal is certainly unwarranted

Risks Inherent in Blood Transfusion The risk inherent in blood transfusion is not inconsiderable In spite of the general knowledge of the danger of

Table 137 TRANSFUSION REACTIONS

Type	Cause	Incidence, %
Pyrogenic	Bacterial pyrogen	1 8–2 9
Urticarial	Sensitivity (?)	0 8–1 1
Serum sickness	Unknown	Rare
Hemolytic	Mismatching of blood	0 1–0
Isoimmunization	Repeated transfusions and pregnancy	Not rare
Circulatory overload	Injudicious augmentation of blood volume	Not rare
Infectious	Grossly contaminated blood	Rare
Transmission of disease	Homologous serum jaundice syphilis malaria	0 4–1 0 Rare
Air embolism	Entry of air into vein via tubing	Rare
Cold reaction	*Cold agglutinins (?)*	Not rare
Hypocalcemia	Exchange transfusions	Not rare
Hemorrhagic diathesis	Massive transfusions	Rare (?)
Fat embolism	Transfusion via bone marrow	Rare

a hemolytic transfusion reaction resulting from mismatching of the major blood group antigens A B and D (Rh) and notwithstanding the care taken to avoid such errors the incidence of hemolytic reactions to blood transfusions is substantial (Table 137) The mortality of hemolytic transfusion reactions is approximately 50 per cent Furthermore as discussed earlier (Chap 45) there is a good chance of immunizing a recipient to one or more of the blood group antigens not tested for in the routine preparation for transfusion It is noteworthy that the risk from sensitization is increased if a woman is transfused with blood from her husband or one of his relatives because of the possibility of her having been previously sensitized during pregnancy to a blood group substance foreign to her but inherent in the fetus There is also the risk of erythroblastosis fetalis in subsequent pregnancies if sensitization occurs as a result of the transfusion

In addition to hemolytic transfusion reactions febrile or pyrogenic anaphylactic and infectious reactions may occur Pyrogenic and urticarial reactions are usually mild and may be induced by small thrombi in the transfused blood soluble toxic substances in new rubber tubing improperly cleaned tubing or insufficiently sterilized solutions which may contain small amounts of bacterial pyrogen Of great seriousness are reactions due to the administration of blood heavily laden with dead or viable bacteria which have gained access to the blood by accident Serum hepatitis is another serious and not completely avoidable complication of blood transfusion There is also the possibility of transmission of malaria or of syphilis but this can usually be avoided by appropriate inquiry and examination of the donor

Before subjecting a patient to blood transfusion thought should be given to his cardiovascular status In all persons with impaired cardiac function the administration of whole blood or other osmotically active solutions must be made cautiously and slowly since an increase in venous pressure and pulmonary edema are easily produced Particular care should be used in regard to concentrated serum albumin because of its capacity to withdraw fluid from the tissues into the circulation Such patients furthermore should be propped in a sitting position during the transfusion The so called "speed reaction" is the result of circulatory overloading and its manifestations are those of right sided *heart failure* It is produced by overrapid infusion in relation to the cardiovascular reserve of the patient and can be prevented by slow administration of blood If the purpose of transfusion is to raise the concentration of circulating hemoglobin rather than to increase the total blood volume red cell suspensions are as effective as are whole blood transfusions and offer the advantage that the volume of injected material is relatively small When it is not convenient to prepare red cell suspensions 60 to 80 per cent of the plasma can be withdrawn from the blood after spontaneous or mechanical sedimentation of the red cells thereby reducing the volume of injected material as well as its salt content

Patients who have *received many* transfusions may develop cold agglutinins and may react with a chill if blood is given without being warmed Sometimes allowing the blood to stand at room temperature is adequate but in many instances it is necessary to have some of the transfusion tubing rest in a water bath maintained at body temperature thus allowing the blood to be warmed before it enters the patient's vein Another complication which may develop in those subjected to repeated transfusions is sensitivity to a heat labile constituent *of fresh normal* plasma In such patients only well washed red cells can be used in transfusion

Except in emergency it is always wise to give the first 50 ml of blood slowly and under the scrutiny of a doctor or nurse In addition it is well whenever possible to wait 30 min in order to determine whether a reaction will occur Fatal transfusion reactions have occurred only when more than 300 ml of blood has been given It is unwise to use blood for transfusion which has been brought to room temperature cooled and then rewarmed since the likelihood of an infectious reaction is thereby increased

Universal Donor While the use of group O blood (universal donor) for general transfusion purposes is undesirable in certain types of hospitals which use transfusion therapy almost exclusively on an *emergency basis the practice* is followed In such situations the two chief hazards should be kept in mind One is the danger of mistyping A_2 donors as group O an error which can be eliminated by

serum or back typing The second danger that of the group O person whose serum contains high titers of anti A and anti B or both is met in part by attempting to discover and screen out such donors and in part by adding A and B substances to the group O blood

271 TREATMENT OF SHOCK

In the management of a patient with shock two general groups of procedures are essential The first involves the attempt to treat the cause and depending on the situation may involve control of bleeding management of diabetic coma treatment of an overwhelming infection etc The second involves the treatment of the circulatory disorder *per se*

When a patient has suffered a known cause of shock e g hemorrhage excessive vomiting *diarrhea trauma etc* it is not difficult to be on the alert for early manifestations increasing heart rate *restlessness faintness in the upright position* In a person who is seen for the first time and when the history is obscure as in some patients with *severe infections it may* be difficult to determine whether or not incipient shock is present

The classic circulatory signs do not usually develop until the venous return and the cardiac output have already undergone serious reduction When the skin is cold and moist (clammy) it is not usually necessary to search for other signs However patients with diabetic coma or other dehydrated states may have dry skin despite peripheral circulatory failure One of the earlier manifestations of shock is likely to be a decline of the blood pressure when the patient changes from the recumbent to the sitting posture This sign is more significant in young than in elderly patients Another relatively early sign particularly valuable in the postoperative state is the presence of a low urine volume—less than 25 ml per hr—despite an adequate intake of water and in the absence of significant fluid loss by extrarenal channels

Once it is recognized that circulatory failure is present or imminent the next problem is the decision as to whether the heart or the periphery is at fault (Chap 14) The cardiac disorders most likely to be confused with peripheral failure are painless coronary occlusion and ectopic tachycardia These and other causes of sudden heart failure should be excluded before vigorous fluid therapy is initiated

General Measures Either the flat or the Trendelenburg position may be preferred Significant elevation of body temperature i e to levels of 102 F or higher should be combated by sponging fans or wet sheets Pain should be relieved by narcotics with the realization that absorption destruction and excretion of drugs are likely to be impaired Oxygen is probably of some value and may be administered as described on p 1773

Administration of Fluid The fluid employed should replace that which is lacking and may be whole blood plasma plasma volume expander or solutions of electrolytes (Chaps 48 49 and p 1776) Intravenous administration of electrolyte free solutions of glucose is also indicated in order to provide water for insensible loss and for urine volume The fluids of choice are blood when shock is due to hemorrhage plasma and saline when burns are responsible a combination of blood and plasma when there is trauma while the shock due to loss of extracellular fluid should be treated by the use of the appropriate protein free electrolyte containing fluid

When doubt exists as to the type of solution for administration it is well to start with blood and to change to plasma or other solutions if the hematocrit subsequently becomes abnormally high When shock is severe the administration of blood should be continued at the rate of about 1 liter per hour for 3 or 4 hr The transfusion is terminated when the signs of shock have disappeared and when a free flow of urine (40 ml or more per hour) has appeared The development of gallop rhythm tachypnea venous distention increase in venous pressure rales at the bases or labored breathing *usually contraindicate further intravenous therapy* If the shock state is still present despite these phenomena it will usually be wise to reduce the rate of the infusion to that needed for the administration of vasopressor drugs to add *Digitalis lanata* (1 2 to 2 0 mg Cedilanid intravenously in about 2 hr) to the infusion fluid to elevate the patient s head and to administer oxygen

As soon as the state of shock has been brought under control isotonic (6 per cent) glucose solution should be administered in order to compensate for insensible loss of water The amount needed for this purpose is usually about 1 liter each 24 hr Since the storage of glucose as glycogen involves the transfer of potassium to the intracellular compartment it is often wise to add potassium chloride (3 Gm per liter) to the infusion fluid However this should not be done if oliguria is present When shock is due to diabetic coma potassium salts are especially important because of the migration of potassium into the cells as insulin induced glycogenesis occurs

Vasopressor Drugs Vasopressor drugs are indicated in all types of severe shock and in the milder instances when shock is known to be the result of

primary vasodilatation e g shock following spinal anesthesia or injury to the spinal cord

Of the several vasopressor drugs norepinephrine is the most potent vasoconstrictor It should be given only by intravenous infusion the utmost care being taken to avoid infiltration of the subcutaneous tissues since necrosis and sloughing of the skin are likely to ensue [should extravasation occur 5 mg phentolamine (Regitine) diluted in 20 ml water and infiltrated throughout the involved tissues has been found to prevent necrosis] Five to fifteen milliliters of a 1 1 000 solution are added to 1 liter of infusion fluid which is administered initially at a rate of 20 to 40 drops per minute The rate of infusion is then varied so as to maintain the blood pressure at a level approaching the preshock level of the patient It should be remembered that a systolic pressure of 120 mm Hg may represent serious hypotension in an elderly person with previous hypertension

Other vasopressor drugs enumerated in their descending order of effectiveness may be used metaraminol (Aramine) mephentermine (Wyamine) methoxamine (Vasoxyl) and phenylephrine (Neo synephrine) They may be administered subcutaneously or intramuscularly in doses of 3 to 15 mg or more approximately every 15 min the exact dose and frequency of administration depending on the behavior of the blood pressure or they may be given by intravenous infusion in concentrations of 30 to 200 mg per liter

Intravenous pressor drugs should be employed only when a physician or nurse is constantly at the bedside watching the patient the blood pressure and the urine volume and altering the rate of infusion according to the response

272 MANAGEMENT OF THE COMATOSE, THE DELIRIOUS, AND THE DEMENTED PATIENT

The various states of disturbed mental function regardless of their cause are often fatal because they not only represent an advanced stage of many diseases but also add their own characteristic burden to the primary disease The main objective in therapy is of course to find the cause—according to the procedures already outlined—and to remove it It often happens however that the disease process is one for which there is no specific therapy or as in hypoxemia or hypoglycemia it may already have expended itself before the patient had access to medical care Again the problem may be infinitely more complex for the disturbance of cerebral function may not be attributable to a single cause but rather be due to several possible factors acting in unison no one of which could account for the total clinical picture In lieu of direct therapy supportive measures must be used and indeed it may be said that chances of surviving the original disease often depend in large measure on their effectiveness The main essentials in the symptomatic management of the delirious demented and comatose patient are presented in Chaps 33 and 36

Care of the Comatose Patient The physician must give attention to every vital function in the insensate patient The following is a brief outline of the more important procedures In order for them to be carried out successfully a well coordinated team of nurses under the constant guidance of a physician is needed

1 If the patient is in shock this demands precedence over all other abnormalities The treatment of shock is discussed in Chap 271

2 Shallow and irregular respirations and cyanosis require the establishment of a clear airway and oxygen The patient should be placed in a semiprone position so that secretions and vomitus do not enter the tracheobronchial tree Pharyngeal reflexes are usually suppressed and therefore an endotracheal tube can be inserted without difficulty Stagnant secretions should be removed with a suction apparatus as soon as they accumulate since they will lead to atelectasis and bronchopneumonia Oxygen can be administered by mask in a 100 per cent concentration for 6 to 12 hr alternating with 50 per cent concentration for 4 hr The depth of respiration can be increased by the use of 5 to 10 per cent CO_2 for periods of 3 to 5 min every hour Atropine should not be given edema of the lungs and fluid in the tracheobronchial passages are not glandular secretions Furthermore atropine thickens this fluid and also may disturb temperature regulation of the body Aminophylline is helpful in controlling Cheyne Stokes breathing Respiratory paralysis dictates the use of a tank type respirator or electrophrenic stimulator but in the authors experience neither has been effective in comatose states in which there is disorganization of respiratory centers

3 The temperature regulating mechanisms may be disturbed and extreme hypothermia or hyperthermia or an unrecognized poikilothermia may occur In hyperthermia removal of blankets and use of alcohol sponges and cooling solutions are indicated

4 The bladder should not be permitted to become distended If the patient does not void a retention catheter should be inserted If more than

500 ml of urine is found in the bladder decompression must be carried out slowly over a period of hours Urine excretion should be kept above 800 to 1 000 ml per day The patient should not be permitted to lie in a wet or soiled bed

5 Diseases of the central nervous system may upset the control of water glucose and salt The unconscious patient can no longer adjust his intake of food and fluids by hunger and thirst Salt losing and salt retaining syndromes have both been described with brain disease Water intoxication severe hypopotassemia or hyperpotassemia or hyponatremia may of themselves prove fatal The maintenance of water and electrolytes has been discussed in Chap 48 If coma is prolonged the insertion of a stomach tube will make the problem of feeding the patient and maintaining fluid and electrolyte balance much easier

6 One should attempt to forestall the development of bronchopneumonia by the prophylactic use of penicillin and streptomycin or some other broad spectrum antibiotic and should watch the legs each day for signs of phlebothrombosis

7 If the patient is capable of moving suitable restraints should be used to prevent a possible fall out of bed

8 Convulsions should be controlled by measures outlined in Chap 35

Care of the Delirious Patient There is an advantage to treating the delirious patient in a general hospital because he often suffers from a medical disease which can be dealt with more adequately there than in a psychiatric hospital Furthermore a delirium seldom lasts more than a few days and if the patient can be kept on a medical ward the social stigma which attaches to incarceration in a mental institution is avoided In the authors experience only a few delirious patients are so agitated and noisy as to annoy others if this does happen many general hospitals now have some facilities for isolating the mentally disturbed patient Delirium of this severity is rare in infectious diseases but is of course not infrequent in alcoholism (delirium tremens) drug intoxication and other medical diseases

The first objectives are to quiet the patient and protect him against injury A private nurse an attendant or a member of the family should be with the patient at all times if this can be arranged Depending on how active and confused the patient is various types of restraint must be employed If he is extremely active and vigorous a locked room screened windows that cannot be opened by the patient and a low bed or mattress on the floor should be arranged It is often better to let the patient walk about the room than to tie him into bed this may excite or frighten him so that he struggles to the point of complete exhaustion and collapse If he is less active the patient can usually be kept in bed by leather wrist restraints a restraining sheet or a net thrown over the bed Unless it is contraindicated by the primary disease the patient should be permitted to sit up or walk about the room part of the day

All drugs that could possibly be responsible for delirium—particularly opiates barbiturates bromides atropine hyoscine cortisone adrenocorticotropic hormone (ACTH) and salicylates in large doses—should be discontinued Paraldehyde and chloral hydrate are the only sedatives that can be trusted under these circumstances Paraldehyde which is preferred may be given orally or rectally in doses of 10 to 12 ml For oral administration mixing it with fruit juices makes it more palatable though alcoholic patients will take it in any form and seem to enjoy it One must be cautious in attempting to suppress the agitation completely To accomplish this may require the use of very large doses of drugs and vital functions may be dangerously impaired The purpose of sedation is to assure rest and sleep so that the patient does not exhaust himself Continuous warm baths or warm packs are also effective in quieting the delirious patient but very few general hospitals have proper facilities for this valuable method of treatment

A fluid intake and output chart should be kept and any fluid and electrolyte deficit should be corrected according to the methods outlined in Chap 48 The pulse and blood pressure should be recorded at intervals of 2 hr in anticipation of circulatory collapse which is sometimes the cause of death particularly in delirium tremens In the event of circulatory collapse transfusions of whole blood and vasopressor drugs may be lifesaving

Finally the physician should be aware of many small therapeutic measures which may allay fear and suspicion and reduce the tendency to hallucinations The room should be kept well lighted and if possible the patient should not be moved from one room to another Every procedure should be explained in detail even such simple ones as the taking of blood pressure or temperature The presence of a member of the family may be a means of enabling the patient to maintain contact with reality

It may be some consolation and also a source of professional satisfaction to remember that most delirious patients tend to recover if placed in good hygienic surroundings and competently nursed The family should be reassured on this point They must also understand that the abnormal behavior and irrational actions of the patient are not willful but rather are symptomatic of a brain disease

primary vasodilatation e g shock following spinal anesthesia or injury to the spinal cord

Of the several vasopressor drugs norepinephrine is the most potent vasoconstrictor It should be given only by intravenous infusion the utmost care being taken to avoid infiltration of the subcutaneous tissues *since necrosis and sloughing of the skin are* likely to ensue [should extravasation occur 5 mg phentolamine (Regitine) diluted in 20 ml water and infiltrated throughout the involved tissues has been found to prevent necrosis] Five to fifteen milliliters of a 1 1 000 solution are added to 1 liter of infusion fluid which is administered initially at a rate of 20 to 40 drops per minute The rate of infusion is then varied so as to maintain the blood pressure at a level approaching the preshock level of the patient It should be remembered that a systolic pressure of 120 mm Hg may represent serious hypotension in an elderly person with previous hypertension

Other vasopressor drugs enumerated in their descending order of effectiveness may be used metaraminol (Aramine) mephentermine (Wyamine) methoxamine (Vasoxyl) and phenylephrine (Neo synephrine) They may be administered subcutaneously or intramuscularly in doses of 3 to 15 mg or more approximately every 15 min the exact dose and frequency of administration depending on the behavior of the blood pressure or they may be given by intravenous infusion in concentrations of 30 to 200 mg per liter

Intravenous pressor drugs should be employed only when a physician or nurse is constantly at the bedside watching the patient the blood pressure and the urine volume and altering the rate of infusion according to the response

272 MANAGEMENT OF THE COMATOSE, THE DELIRIOUS, AND THE DEMENTED PATIENT

The various states of disturbed mental function regardless of their cause are often fatal because they not only represent an advanced stage of many diseases but also add their own characteristic burden to the primary disease The main objective in therapy is of course to find the cause—according to the procedures already outlined—and to remove it It often happens however that the disease process is one for which there is no specific therapy or as in hypoxemia or hypoglycemia it may already have expended itself before the patient had access to medical care Again the problem may be infinitely more complex for the disturbance of cerebral function may not be attributable to a single cause but rather be due to several possible factors acting in unison no one of which could account for the total clinical picture In lieu of direct therapy supportive measures must be used and indeed it may be said that chances of surviving the original disease often depend in large measure on their effectiveness The main essentials in the symptomatic management of the delirious demented and comatose patient are presented in Chaps 33 and 36

Care of the Comatose Patient The physician must give attention to every vital function in the insensate patient The following is a brief outline of the more important procedures In order for them to be carried out successfully a well coordinated team of nurses under the constant guidance of a physician is needed

1 If the patient is in shock this demands precedence over all other abnormalities The treatment of shock is discussed in Chap 271

2 Shallow and irregular respirations and cyanosis require the establishment of a clear airway and oxygen The patient should be placed in a semiprone position so that secretions and vomitus do not enter the tracheobronchial tree Pharyngeal reflexes are usually suppressed and therefore an endotracheal tube can be inserted without difficulty Stagnant secretions should be removed with a suction apparatus as soon as they accumulate since they will lead to atelectasis and bronchopneumonia Oxygen can be administered by mask in a 100 per cent concentration for 6 to 12 hr alternating with 50 per cent concentration for 4 hr The depth of respiration can be increased by the use of 5 to 10 per cent CO_2 for periods of 3 to 5 min every hour Atropine should not be given edema of the lungs and fluid in the tracheobronchial passages are not glandular secretions Furthermore atropine thickens this fluid and also may disturb temperature regulation of the body Aminophylline is helpful in controlling Cheyne Stokes breathing Respiratory paralysis dictates the use of a tank type respirator or electrophrenic stimulator but in the authors experience neither has been effective in comatose states in which there is disorganization of respiratory centers

3 The temperature regulating mechanisms may be disturbed and extreme hypothermia or hyperthermia or an unrecognized poikilothermia may occur In hyperthermia removal of blankets and use of alcohol sponges and cooling solutions are indicated

4 The bladder should not be permitted to become distended If the patient does not void a retention catheter should be inserted If more than

500 ml of urine is found in the bladder decompression must be carried out slowly over a period of hours Urine excretion should be kept above 600 to 1 000 ml per day The patient should not be permitted to lie in a wet or soiled bed

5 Diseases of the central nervous system may upset the control of water glucose and salt The unconscious patient can no longer adjust his intake of food and fluids by hunger and thirst Salt losing and salt retaining syndromes have both been described with brain disease Water intoxication severe hypopotassemia or hyperpotassemia or hyponatremia may of themselves prove fatal The maintenance of water and electrolytes has been discussed in Chap 48 If coma is prolonged the insertion of a stomach tube will make the problem of feeding the patient and maintaining fluid and electrolyte balance much easier

6 One should attempt to forestall the development of bronchopneumonia by the prophylactic use of penicillin and streptomycin or some other broad spectrum antibiotic and should watch the legs each day for signs of phlebothrombosis

7 If the patient is capable of moving suitable restraints should be used to prevent a possible fall out of bed

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Care of the Demented Patient Dementia is a clinical state of the most serious nature and usually it is worthwhile to admit the patient to a hospital for a period of observation The physician then has an opportunity to see the patient several times in a new and fairly constant hospital environment and certain special procedures such as x rays of the skull lumbar puncture analysis for blood bromides basal metabolic rate and electroencephalogram can be carried out at this time The management of the demented patient in the hospital may be relatively simple if he is quiet and cooperative If the disordered mental function is severe a nurse attendant or member of the family must stay with him at all times Provision must be made for adequate food and fluid intake and control of infection using the same measures outlined for the delirious patient

Once it is established that the patient has an untreatable dementing brain disease a responsible member of the family should be apprised of the medical facts The patient should be told that he has a nervous condition for which he is to be given rest and treatment Nothing is accomplished by telling him more The family should be given the prognosis if the diagnosis is sufficiently certain for this to be possible If the dementia is slight and circumstances are suitable the patient may remain at home continuing activities of which he is capable He should be spared responsibility and be guarded against injury which might result from imprudent action If he is still at work plans for occupational retirement should be carried out If the home situation is unsuitable or when in the more advanced stages of the disease mental and physical enfeeblement become pronounced institutional care should be advised Seizures should be treated symptomatically Nerve tonics vitamins and hormones are of no value in checking the course of the illness or in regenerating decayed tissue They may however offer moral support for the patient and the family

The treatment of the coma associated with recurrent convulsions is discussed on pp 334 to 336

273 RESPIRATORY DISTURBANCES

T R Harrison and Ben V Branscomb

COUGH

The treatment of cough is considered on p 1386 in the discussion of chronic bronchitis The management of episodes of acute respiratory insufficiency in patients with chronic pulmonary disease has likewise been previously considered (p 1392) Acute pulmonary edema is discussed on p 1307 The discussion to follow deals with the management of those respiratory disturbances which may occur in almost any gravely ill patient

Measures to Secure a Clear Airway The cough reflex is depressed in moribund individuals and in patients under the effect of opiates or general anesthesia Persons with myasthenia gravis or poliomyelitis or indeed any severe debilitating disease may not be able to cough effectively because of weak muscular action The problem of bronchial drainage then becomes a matter of greatest urgency—of life or death—since retained mucus and bacteria will cause atelectasis and pneumonia

Measures to facilitate bronchial drainage in weakened and debilitated patients include elevation of the lower part of the body frequent turning and clearing of the pharynx by mechanical suction through a soft rubber catheter In most patients it is even possible to pass the suction tip of the catheter into the larynx trachea and main bronchi—a relatively simple and sometimes supremely important procedure which every physician should learn to do In patients whose cough mechanism is likely to be ineffective for some days e g in poliomyelitis tetanus or after a cerebrovascular accident tracheotomy may be performed to permit frequent clearing of the upper bronchial tree by suction Tracheotomy reduces the dead space by about one fourth and thus makes breathing more efficient

Mechanical devices are being developed which can increase the effectiveness of cough in weakened individuals They make use of positive pressure distention of the air passages followed by rapid reduction of pressure and result in a forceful exhalation almost as effective as a normal cough

Mechanical Aids to Respiration One of the most difficult decisions involved in the management of patients with diseases which embarrass or threaten respiration is whether or not to use some type of respirator To be placed in an iron lung is terrifying and one hesitates to subject the patient to the experience unless he is certain that it is necessary in order to save life On the other hand delay in the use of the respirator until the patient has become dyspneic and cyanotic may result in atelectasis and pneumonia which cannot then be corrected by the use of the respirator The patient often does not know when he is in need of assistance in respiration Useful warnings of respiratory difficulty are breathlessness upon attempting to talk and inability to count to 15 at 1 sec intervals on a single breath The standard basal metabolic rate machine is a useful device for recording the volume of each respiration on quiet breathing and on maximal

effort A tidal volume of less than 300 ml and a vital capacity of less than 500 ml indicate impending respiratory failure

The tank type respirator is the most generally used and reliable method An alternative procedure is the use of positive pressure supplied through a tracheotomy or an endotracheal tube by anesthesia apparatus or any of several automatic intermittent positive pressure machines

OXYGEN THERAPY

Indications *Acute cyanosis* of recent origin resulting from arterial hypoxia constitutes the most urgent indication for oxygen Cyanosis due to abnormal blood pigment or to arterial hypoxia brought about by venoarterial shunts is not an indication The situation is more complex in patients with chronic arterial hypoxia of pulmonary origin this is discussed on p 1392

Oxygen is of great value in patients with acute pulmonary edema but is rarely of much benefit in patients with chronic congestive failure unless cyanosis is pronounced

There is some doubt as to whether oxygen should be used routinely in patients with shock or with myocardial infarction who display little or no cyanosis or dyspnea If the arterial blood is already normally saturated one cannot increase the oxygen content much by breathing oxygen

Contraindications Aside from the expense involved and the possible psychologic disadvantages the only important contraindication to oxygen is the presence of well marked respiratory acidosis with compensatory rise in bicarbonate (p 1392)

Technical Considerations Rarely is it important to administer oxygen in concentrations greater than 40 per cent This may be achieved by a flow rate of 8 to 10 liters a minute of *humidified* oxygen using a nasal catheter a mask or a tent as dictated by the circumstances The catheter should not be used in the nose or the trachea of patients who have been subjected to tracheotomy

HICCOUGH

The following simple measures may be tried holding the breath drinking a large glass of water building up carbon dioxide in the tissue by rebreathing into a paper bag or through 3 ft of garden hose or inhalation of 5 to 10 per cent carbon dioxide relief of abdominal distention pressure on the eyeballs irritating the nose to produce a sneeze inducing nausea or vomiting by tickling the throat and pressure over the carotid sinus or over the phrenic nerves If there is gastric irritability lavage of the stomach and relief of any distention followed by administration of aluminum hydroxide or magnesium trisilicate (Gelusil) 4 to 8 ml every 2 to 4 hr may be helpful Mucosal reflex activity may be suppressed by a 0 5 per cent solution of cocaine hydrochloride in water given in a dose of 4 ml in a glass of water every hour for four doses Nupercaine lozenges (Nuporals) containing 1 mg Nupercaine may be dissolved in the mouth Occasionally two or three inhalations from a broken ampul of amyl nitrite will quickly end an attack Amphetamine (Benzedrine) sulfate 5 to 10 mg two or three times a day also sometimes gives relief Should the hiccough persist atropine 0 4 mg three or four times a day should be given followed by heavy sedation with pentobarbital 0 2 to 0 4 Gm

If all the above measures fail the phrenic nerve to the leaf of the diaphragm involved (when that can be determined by fluoroscopy) should be blocked with 0 5 per cent procaine Temporary relief by this measure justifies resorting to phrenic nerve crush in exceptionally stubborn cases Patients with emphysema or severe pulmonary or cardiac disease are poor candidates for crushing unless facilities are readily available for intubation artificial respiration and oxygen therapy

Section 3 "Iatrogenic" Disorders

274 "IATROGENIC DISORDERS

This term refers to adverse effects induced by the physician in caring for his patients not only the direct injuries that may result from therapeutic and diagnostic measures but also the hurt that can be inflicted by words or actions The term generally carries with it the connotation of an untoward effect that could have been avoided by exercise of reasonable care and knowledge on the part of the physician

Every medical procedure whether diagnostic or therapeutic contains within it the potentiality of harm and it would be impossible to afford the

patient all the benefits of modern scientific medicine if every legitimate step in diagnosis and therapy were withheld because of the possible risks involved Legitimate" here implies that the physician has weighed the pros and cons for a procedure and has concluded on rational grounds that it is advisable or essential for the relief of discomfort or the cure or amelioration of disease An iatrogenic disorder in the sense that it is here considered is one that is deemed to have ensued when the deleterious effects of the physician s action exceed any advantages that could have reasonably been anticipated

Not only are there unavoidable risks in the use of many of the newer and more potent therapeutic agents even when employed with the utmost caution and intelligence but the task of the physician is multiplied because the rate at which these new agents are introduced is usually more rapid than the pace at which contraindications become clear and understood Even when the need for a drug is indisputable its harmful effects can hardly be viewed with complacence but they are all the more deplorable when a better understanding of the patient s illness and an appreciation of the dubious or negligible indications for the use of a drug or other procedure would have prevented the accident None of the antibiotics is free from disturbing and sometimes dangerous side effects A persistent diarrhea due to a proctitis caused by a broad spectrum antibiotic may be far more distressing than the trivial respiratory infection for which it is prescribed The use of cortisone in a patient with relatively mild arthritis may cause a serious gastric hemorrhage or perforation the activation of a latent tuberculosis or a fatal adrenal crisis if a relatively mild stress is imposed shortly after the withdrawal of the drug Death may occur following an operative procedure when cortisone has been given and then withdrawn just prior to operation It is known that in spite of tropic hormone administration (thyroid stimulating adrenal cortical stimulating or follicle stimulating hormone) several weeks are required before a hypofunctioning gland is restored to normal Fatal homologous serum jaundice may follow the needless transfusions of plasma or blood and serious depression of the bone marrow may result from a large variety of drugs It is difficult to condone these and other catastrophes when the advantages expected of the offending agents could hardly have been commensurate with the risks inherent in their use Too often a serious accident has followed the use of a therapeutic agent when the physician at a loss for a diagnosis or a logical program of management has simply decided upon an ill advised "therapeutic trial" These hazards are likely to increase as patients become more and more informed of the miracles of modern research widely heralded in newspapers radio and television and more likely to demand that new discoveries be made available to them

Ill effects have been known to ensue from the injudicious administration of excessive doses of vitamins Fortunately the widespread use of vitamin mixtures fortified with minerals and other substances in ludicrously microscopic quantities usually involves nothing more serious than a waste of money But estrogens cleverly advertised in even the most reputable medical journals to relieve almost every complaint occurring in a middle aged woman may cause uterine bleeding which aside from being serious in itself inevitably raises the question of possible malignancy and the necessity for a diagnostic curettage Thyroid extract often given without justification and in doses far exceeding the endogenous level of secretory activity of a normal person may precipitate ectopic rhythms or even congestive failure Increasing evidence to incriminate the role of radiation in causing cancer and leukemia should make us wary of blithely ordering x ray therapy for enlarged thymus bursitis annoying but harmless skin disorders and even for diagnostic procedures especially when repeated without sound reason

There is one long standing "iatrogenic" disorder that deserves particular mention habituation to opiates Too often the administration of an opiate to a susceptible patient may initiate a lifelong problem all the more tragic when the need for sedation and relief of pain might have been met successfully by other measures Added caution must be employed in the care of professional associates who have ready access to these drugs The same warning applies to the use of synthetic derivatives of morphine or related substances which are sometimes glibly quoted as being relatively free from the danger of habituation

It is equally important to consider the harm which physicians may do to patients through ill considered or unjustified remarks No matter what the constitutional make up of the patient may be he approaches the physician with at least some degree of fear and concern His anxiety can be enhanced by a too serious demeanor a flippant remark or an impressive conference Particularly is it true that untoward remarks or actions have had ill effects in relation to heart disease Many persons have been crippled by cardiac neurosis because a physician has misinterpreted the significance of a heart murmur or an electrocardiographic finding Even when organic heart disease is present, the patient may be more severely disabled by an unjustified statement regarding prognosis or the imposition of too strict limitation of activity The physician s manner and behavior are important in

their implications to the patient A spirited bedside discussion regarding the interpretation of auscultatory findings may give the false impression that serious heart disease exists Conversely a solemn appearing conclave just out of earshot may cause the patient to conclude erroneously that his prognosis is grave or hopeless Sometimes the patient's pride is unwittingly offended because of his misinterpretation of terms overheard such as "degenerative process" or "neurosis" Similar sounding medical words have been confused e g a patient heard the word "leukopenia" and concluded that he had leukemia

The good physician appreciates the fact that he is always in a position where he may cause injury by his treatment by his words and by his behavior Skill in handling of patients cannot be taught all that one can do is to emphasize the importance of tact caution judgment and wisdom—ideals to be striven for but never fully attained Better than words are the examples of thoughtfulness and understanding that are exhibited by the medical teacher or senior staff physician in his ward or clinic conferences with students and younger colleagues But even if it were possible to finally achieve the goal—a generation of flawless physicians with infallible judgment and infinite wisdom—there would still be the patients who have uncanny capacity for misinterpreting the most innocent remarks and the most cautiously expressed opinions In the end "iatrogenic" illness is largely a matter of incomplete knowledge and fallacious judgment on the part of the physician conjoined with the fears and anxieties of the patient So long as medicine remains an art "iatrogenic" illness will remain The best hope for diminishing its incidence will come from a ceaseless consideration by the physician of the wisdom of each of his decisions and acts and from a greater appreciation of the mood and attitude of the person who consults the physician

patient all the benefits of modern scientific medicine if every legitimate step in diagnosis and therapy were withheld because of the possible risks involved Legitimate here implies that the physician has weighed the pros and cons for a procedure and has concluded on rational grounds that it is advisable or essential for the relief of discomfort or the cure or amelioration of disease An iatrogenic disorder in the sense that it is here considered is one that is deemed to have ensued when the deleterious effects of the physician s action exceed any advantages that could have reasonably been anticipated

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APPENDIX
Laboratory Values of Clinical Importance

Laboratory Values of Clinical Importance

BODY FLUIDS AND OTHER MASS DATA

Body fluid total volume 50% (in obese) to 70% (lean) of body weight
Intracellular Approximately 67% of total
Extracellular 16–20% of body weight

Blood

Total volume Male 69 ml/kg body weight
Female 64 ml/kg body weight
Plasma volume Male 38 ml/kg body weight
Female 37 ml/kg body weight
Red cell volume Male 30 ml/kg body weight (1.15–1.21 L per sq m surface area)
Female 27 ml/kg body weight

$$\text{mEq (milliequivalent)} = \frac{\text{mg/100 ml} \times 10 \times \text{valence}}{\text{atomic weight}}$$

$$\text{mg/100 ml} = \frac{\text{mEq} \times \text{atomic weight}}{10 \times \text{valence}}$$

Atomic Weights of Elements Commonly Encountered in Clinical Medicine

Calcium	40.08	Magnesium	24.32
Carbon	12.01	Nitrogen	14.008
Chlorine	35.46	Oxygen	16.00
Copper	63.54	Phosphorus	30.98
Hydrogen	1.008	Potassium	39.100
Iodine	126.91	Sodium	22.997
Iron	55.85	Sulfur	32.07

CEREBROSPINAL FLUID

Cells <5 per cu mm all lymphocytes
Pressure initial (horizontal position) 0–180 mm water
Calcium 2.24–2.74 mEq/L 4.5–5.5 mg/100 ml
Chloride as Cl^- 120–130 mEq/L 430–460 mg/100 ml
Cholesterol 0.06–0.22 mg/100 ml
Colloidal gold test Not more than one in any tube
Creatinine 0.4–1.5 mg/100 ml
Glucose 50–75 mg/100 ml
Magnesium (average) 2.7 mEq/L 3.3 mg/100 ml
Nonprotein nitrogen 12–30 mg/100 ml
Protein 14–45 mg/100 ml
Potassium 3.5–5.0 mEq/L 13.7–20.0 mg/100 ml
Urea nitrogen 6–15 mg/100 ml

CHEMICAL CONSTITUENTS OF BLOOD

Albumin serum 4.0–5.2 Gm/100 ml
Ammonia, whole blood venous 30–70 μg/100 ml
Amylase whole blood (Somogyi) 60–180 units 100 ml
Ascorbic acid whole blood 0.4–1.0 mg/100 ml
Leukocytes 25–40 mg/100 ml
Base total serum 145–155 mEq/L
Bilirubin total serum (Malloy Evelyn) 0.1–0.8 mg/100 ml
Direct serum 0.1–0.2 mg/100 ml
Indirect serum 0.1–0.6 mg/100 ml
Calcium serum 4.5–6.0 mEq/L 9–11 mg/100 ml
Carbon dioxide–combining power serum 21–28 mEq/L 50–65 vol %
Carbon dioxide content serum 21–30 mEq/L 50–70 vol %
Carbon dioxide tension serum 38–40 mm Hg
Carotenoid serum 100–200 μg/100 ml
Chloride serum (as Cl) 98–106 mEq/L 350–375 mg/100 ml
Cholesterol Total serum (Man Peters method) (mean ± 1 SD) 194 ± 36 mg/100 ml
Esters serum 100–180 mg/100 ml
Cholesterol ester fraction of total cholesterol serum 68–72%
Copper serum (mean ± 1 SD) 114 ± 14 μg/100 ml
Corticoids plasma (Porter-Silber) (mean ± 1 SD) 13 ± 6 μg/100 ml
Creatinine serum (Peters) 1–1.5 mg/100 ml
Fat neutral serum 150–250 mg/100 ml
Fatty acids serum 380–465 mg/100 ml
Fibrinogen plasma 0.2–0.4 Gm/100 ml
Globulin serum 1.3–2.7 Gm/100 ml
Glucose (fasting) blood (Nelson-Somogyi) 60–90 mg/100 ml
Hemoglobin blood (sea level)
Males 14–18 Gm/100 ml
Females 12–16 Gm/100 ml
Icterus index, serum 4–6 units
Iodine protein bound serum 4–8 μg/100 ml
Iron serum males and females (mean ± 1 SD) 105 ± 37.8 μg/100 ml
Iron binding capacity serum (mean ± 1 SD) 339 ± 30.8 μg/100 ml
Ketones total 0.5–1.5 mg/100 ml
Lipase serum (Cherry Crandall) 1.5 ml N/20 NaOH (upper limit of normal)
Lipid phosphorus (Man Peters) (mean ± 1 SD) 9.2 ± 1.4 mg/100 ml
Lipids total serum 500–600 mg/100 ml
Magnesium serum 1.5–3.0 mEq/L 2–3 mg/100 ml
Methemoglobin <1.8 %
Nitrogen nonprotein serum 15–35 mg/100 ml
Oxygen capacity blood 18–22 vol %
Oxygen content Arterial blood 17–21 vol %
Venous blood arm 10–16 vol %
Oxygen per cent saturation (sea level)
Arterial blood 94–96 vol %
Venous blood arm 60–85 vol %
Oxygen tension serum 95–100 mm Hg
pH serum 7.37–7.45
Phosphatase acid total serum Bodansky method 0.2–0.8 unit/100 ml
Gutman or King Armstrong method 1–4 units/100 ml

Kidney

Clearances (corrected to 1.73 sq m body surface area)

Measures of glomerular filtration rate

Inulin clearance (C_I) Males 124 ± 25.8 ml/min

Females 119 ± 12.8 ml/min

Endogenous creatinine 91–130 ml/min

Urea 60–100 ml/min

Measures of effective renal plasma flow and tubular function

Para aminohippuric acid (C_{PAH})

Males 654 ± 163 ml/min

Females 594 ± 102 ml/min

Tubular maximum for *PAH* males and females 77.2 mg/min

Diodrast 600–800 ml/min

20–30% excretion in 15 min

Concentration and dilution test

Specific gravity of urine After 12 hr fluid restriction 1.025 or more

After 12 hr water intake 1.003 or less

Phenolsulfonphthalein After intramuscular injection

Excretion in urine in 15 min 25% or more

Excretion in urine in 2 hr 55–75%

After intravenous injection

Excretion in urine in 2 hr 55–75%

Specific gravity maximal 1.022–1.028

Tubular reabsorption phosphorus

79–94% of filtered load

Metabolic

Basal metabolic rate −10% to +10% of mean standard

Creatine tolerance 0% ingested creatine retained in adults

Glucose tolerance 100 Gm glucose or 1.75 Gm glucose/kg body weight p.o. Blood sugar not more than 160 mg/100 ml after 1 hr return to normal in 2 hr sugar not present in any urine specimen

Radioactive iodine (I^{131}) Uptake 20–50% of administered dose

Excretion 30–70% of administered dose in 24 hr following tracer dose provided renal function is normal

Protein bound serum or plasma <0.3% of administered dose/l plasma at 72 hr following tracer dose

Conversion ratio <3 % at 24 hr

Water test (Saffer) 80% excretion of a 1,500 ml water load in 4 hr

HEMATOLOGIC EXAMINATIONS

(See also Chemical Constituents of Blood)

Bone Marrow (See Table 13, p. ?)

Erythrocytes (See Table below)

NORMAL VALUES AT VARIOUS AGES

Age	Red cell count millions per cu mm	Hemoglobin Gm per 100 ml	Vol packed RBC ml per 100 ml	Corpuscular values			
				MCV cu μ	MCH γγ	MCHC %	MCD μ
First day	5.1 ± 1.0	19.5 ± 5.0	54.0 ± 10.0	106	38	36	8.6
2–3 days	5.1	19.0	53.5	105	37	35	
4–8 days	5.1	18.3 ± 4.0	52.5	103	36	35	
9–13 days	5.0	16.5	49.0	98	33	34	
14–60 days	4.7 ± 0.9	14.0 ± 3.3	42.0 ± 7.0	90	30	33	8.1
3–5 months	4.5 ± 0.7	12.2 ± 2.3	36.0	80	27	34	7.7
6–11 months	4.6	11.8	35.5 ± 5.0	77	26	33	7.4
1 year	4.5	11.2	35.0	8	25	32	7.3
2 years	4.6	11.5	35.5	77	25	32	
3 years	4.5	12.5	36.0	80	27	35	7.4
4 years	4.6 ± 0.6	12.6	37.0	80	27	34	
5 years	4.6	12.6	37.0	80	27	34	
6–10 years	4.7	12.9	37.5	80	2	34	7.4
11–15 years	4.8	13.4	39.0	82	28	34	
Adults							
Females	4.8 ± 0.6	14.0 ± 2.0	42.0 ± 5.0	87 ± 5	29 ± 2	34 ± 2	7.5 ± 0.3
Males	5.4 ± 0.8	16.0 ± 2.0	47.0 ± 7.0	87 ± 5	29 ± 2	34 ± 2	7.5 ± 0.3

MCV = mean corpuscular volume MCH = mean corpuscular hemoglobin MCHC = mean corpuscular hemoglobin concentration MCD = mean corpuscular diameter (Wintrobe *Clinical Hematology* 4th ed Philadelphia Lea & Febiger 195?)

Phosphatase acid tartrate sensitive (Fishman Lerner)
<0.6 unit/100 ml

Phosphatase alkaline serum Bodansky method
1–4 units/100 ml
King Armstrong method 8–13 units/100 ml

Phospholipids serum 150–250 mg/100 ml

Phosphorus inorganic serum 1–1.5 mEq/L
3–4.5 mg/100 ml

Potassium serum 3.5–5.0 mEq/L 13.7–20.0 mg/100 ml

Proteins total serum 6.5–8.0 Gm/100 ml

Proteins electrophoretic fractions (Tiselius)

	Plasma %	*Serum* %
Albumin	55.2	58 ± 3
Globulins α_1	5.3	5 ± 2
α_2	8.7	12 ± 3
β	13.4	11 ± 4
Fibrinogen	6.5	
Globulins γ_1 }	11.0	2 ± 2
γ_2		12 ± 3

Prothrombin plasma (Quick method)
11–12 sec (cf control)

Sodium serum 132–142 mEq/L
303–327 mg/100 ml (as sodium)
771–832 mg/100 ml (as sodium chloride)

Sulfates inorganic serum 0.5–1.5 mg/100 ml

Urea nitrogen whole blood 10–20 mg/100 ml

Uric acid serum enzymatic method (Praetorius) (mean ± 1 SD)
Males 5.0 ± 1.2 mg/100 ml
Females 3.8 ± 0.9 mg/100 ml

Uric acid serum (Talbot) 2.5–5.0 mg/100 ml

Vitamin A serum 50–100 μg/100 ml

FUNCTION TESTS

Liver

Bromsulphalein (5 mg/kg body weight IV)
5% or less retention at end of 45 min

Cephalin-cholesterol flocculation 0 or + at 48 hr

Galactose tolerance after ingestion of 40 Gm
Excretion of not more than 3 Gm in urine in 5 hr

Hippuric acid *After ingestion of 6 Gm sodium benzoate*
Excretion of 3–3.5 Gm hippuric acid in urine in 4 hr
After injection of 1.77 Gm sodium benzoate IV
Excretion of 0.70 Gm hippuric acid in urine in 1 hr

Prothrombin test Increase of 15% or more in prothrombin concentration in blood in 24 hr after injection of synthetic vitamin K

Serum glutamic oxalacetic transaminase (SGOT)
(mean ± 1 SD) 22 ± 7 units/ml/min

Serum glutamic pyruvic transaminase (mean ± 1 SD)
16 ± 9 units/ml/min

Thymol turbidity 3 units or less

Urobilinogen
Urine Semiquantitative (2 hr) 0.5–1.5 units
Quantitative 1–3.5 mg/24 hr
Stool Semiquantitative (per 100 Gm) <350 units
Quantitative 40–280 mg/24 hr

Zinc sulfate turbidity <4 units

Circulation

Cardiac output (Fick) 3.3 L/sq m/min

Circulation time Arm to lung ether 4–8 sec
Arm to tongue calcium gluconate 12–18 sec
Decholin 10–16 sec
Saccharin 9–16 sec

Pressures intracardiac and intraarterial
Aorta Systole 120 mm Hg
Diastole 80 mm Hg
Atrium Left (mean) 5 mm Hg
Right (mean) 2 mm Hg
Pulmonary artery Systole 25 mm Hg
Diastole 10 mm Hg
Wedge (mean) 9 mm Hg
Ventricle left Systole 120 mm Hg
Diastole 5 mm Hg
Ventricle right Systole 25 mm Hg
Diastole 0 mm Hg
Venous (antecubital) 70–140 mm H_2O

Gastrointestinal

Gastric juice basal Free acid
5–25 units (ml N/10 alkali per 100 ml gastric fluid)
Total acid 5–10 units higher than free acid
Volume (fasting) 5–150 ml
Chlorides (as Cl) (mean and range)
104 (24–127) mEq/L
HCl free 200 mg/100 ml
Reaction as pH 1.6–1.8
Volume 24 hr 2–3 L
Following standard meal Free acid 20–70 units
Total acid 10 units higher than free acid
Volume in 1 hr 50–100 ml
Following alcohol meal Maximum free acid [illegible]0 units
Maximum total acid 85 units

Jejunal secretion fasting Chloride 80–140 mEq/L
HCO_3 2–32 mEq/L
Total base 110–160 mEq/L

Pulmonary

Maximum breathing capacity L/min
Males
86.5 − (0.522 × age in yr) × body surface in sq m
Females
71.3 − (0.474 × age in yr) × body surface in sq m

Residual volume 1.0–1.5 L

Vital capacity (*VC*) total
Males
4–6 L (27.63 − (0.112 × age in yr) × ht cm)
Females
3–4.5 L (21.78 − (0.101 × age in yr) × ht cm)
Timed 1 sec 80% of total
3 sec 93% of total

Total capacity (supine) in ml $\frac{VC}{80} \times 100$ at 16–34 yr

$\frac{VC}{76.6} \times 100$ at 35–49 yr $\frac{VC}{69.2} \times 100$ at 50–69 yr

$\frac{\text{Residual volume}}{\text{total capacity}} \times 100$ 20.0 at 16–34 yr
23.4 at 35–49 yr 30.8 at 50–69 yr

Erythrocytes (continued)

Fragility, osmotic: Slight hemolysis 0.45–0.39%
  Complete hemolysis 0.33–0.30%
Hemochromogens in plasma: 3–5 mg/100 ml
 Life span: Normal survival 120 days
  Chromium half life (T ½) 28 days
Plasma iron turnover rate: 38 mg/24 hr (0.47 mg/kg)
Protoporphyrin, free erythrocyte (F.E.P.):
  20–38 μg/100 ml RBCs
Reticulocytes: 0.5–2.0% of red cells
Sedimentation rate: Westergren: <15 mm/1 hr
 Wintrobe: Male 0–9 mm/1 hr
  Female 0–20 mm/1 hr

Leukocytes

NORMAL VALUES

	Per cent	Average	Minimum	Maximum
Total number per cu mm		7,000	5,000	10,000
Neutrophils				
Juvenile	3–5	300	150	400
Segmented	54–62	4,000	3,000	5,800
Eosinophils	1–3	200	50	250
Basophils	0–0.75	25	15	50
Lymphocytes	25–33	2,100	1,500	3,000
Monocytes	3–7	375	285	500

Platelets and Coagulation

Platelets per cu mm: direct counting method
 200,000–300,000
Bleeding time (Ivy method): majority and range
 1–5 min, 0–12 min
Clot retraction time: Begins in 30 min, complete in less than 24 hr, usually <6 hr
Coagulation time (Lee-White method):
 majority and range: 5–15 min, 2–19 min

Schilling Test

Excretion in urine of orally administered radioactive vitamin B_{12} following flushing parenteral injection of B_{12}: 7–22%

STOOL

Bulk: 100–200 Gm daily
Dry matter: 23–32 Gm (4–38% of fresh feces)
Fat, on unregulated diet: Total 7–25% of dry matter
 Neutral: 2.5–12% of dry matter, 25–60% of total fat
Fatty acid: Free 1–10% of dry matter
 Combined as soap 0.5–12% of dry matter
Nitrogen excretion: <1.7 Gm/day
Protein content: Minimal
Urobilinogen: 40–280 mg/24 hr
Water: Approximately 65%
Coproporphyrin: 400–1,000 μg/24 hr

URINE

Acidity, titratable: 125–150 mEq/24 hr
α-Amino nitrogen: 0.4–1.0 Gm/24 hr
Ammonia: 30–50 mEq/24 hr
Amylase (Somogyi): 260–950 mg of glucose/24 hr
Calcium: 10 mEq or 200 mg calcium diet:
  <7.5 mEq/24 hr or <0.15 Gm/24 hr
Copper: 0–25 μg/24 hr
Coproporphyrins (types I and III): 100–300 μg/24 hr
Creatine, as creatinine: Adult males <50 mg/24 hr
 Adult females <100 mg/24 hr
Creatinine: 1.0–1.6 Gm/24 hr
Estrogens (Jailer method): Male 5–20 μg/24 hr
 Female (nonpregnant):
  15–100 μg/24 hr depending on time of menstrual cycle
Glucose, true (oxidase method): 50–300 mg/24 hr
Ketones, total (mean ± 1 SD): 50.5 ± 30.7 mg/24 hr
17-Ketosteroids (Holtorf-Koch method):
 Male 8–20 mg/24 hr
 Female 6–15 mg/24 hr
11-Oxysteroid, or corticoids (Porter-Silber method):
  2.2–8.0 mg/24 hr
Protein: <50 mg/24 hr
Urobilinogen: 1–3.5 mg/24 hr